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1. Your reference

46831.GB02/JMD

2. Patent application number

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0417436.3

3. Full name, address and postcode of the or of each applicant (*underline all surnames*)

Cambridge University Technical Services Limited  
The Old Schools  
Trinity Lane  
Cambridge  
CB2 1TS

Patents ADP number (*if you know it*)

6956809004

If the applicant is a corporate body, give the country/state of incorporation

United Kingdom

4. Title of the invention

Anti-Inflammatory Agents

5. Full name, address and postcode in the United Kingdom to which all correspondence relating to this form and translation should be sent

Reddie & Grose  
16 Theobalds Road  
LONDON  
WC1X 8PL

Patents ADP number (*if you know it*)

91001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (*if you know it*) the or each application number

Country

Priority application  
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Date of filing  
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7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing  
(day/month/year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

- a) any applicant named in part 3 is not an inventor, or
- b) there is an inventor who is not named as an applicant, or
- c) any named applicant is a corporate body.

See note (d))

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Translations of priority documents	0
Statement of inventorship and right to grant of a patent ( <i>Patents Form 7/77</i> )	0
Request for preliminary examination and search ( <i>Patents Form 9/77</i> )	0
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Any other documents <i>(please specify)</i>	0

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11. I/We request the grant of a patent on the basis of this application.

Signature(s)

*Reddie & Grose*

Date 4 August 2004

12. Name and daytime telephone number of person to contact in the United Kingdom

DR J. M. DAVIES  
01223 360 350

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### Anti-Inflammatory Agents

The invention relates to the use of 3-aminocaprolactam derivatives for preparing a medicament intended to prevent or treat inflammatory disorders.

Inflammation is an important component of physiological host defence.

- 5 Increasingly, however, it is clear that temporally or spatially inappropriate inflammatory responses play a part in a wide range of diseases, including those with an obvious leukocyte component (such as autoimmune diseases, asthma or atherosclerosis) but also in diseases that have not traditionally been considered to involve leukocytes (such as osteoporosis or Alzheimer's disease).

10

The chemokines are a large family of signalling molecules with homology to interleukin-8 which have been implicated in regulating leukocyte trafficking both in physiological and pathological conditions. With more than fifty ligands and twenty receptors involved in chemokine signalling, the system has the requisite

- 15 information density to address leukocytes through the complex immune regulatory processes from the bone marrow, to the periphery, then back through secondary lymphoid organs. However, this complexity of the chemokine system has at first hindered pharmacological approaches to modulating inflammatory responses through chemokine receptor blockade. It has proved difficult to determine which  
20 chemokine receptor(s) should be inhibited to produce therapeutic benefit in a given inflammatory disease.

More recently, a family of agents which block signalling by a wide range of chemokines simultaneously has been described: Reckless et al., Biochem J. (1999)

- 25 340:803-811. The first such agent, a peptide termed "Peptide 3", was found to inhibit leukocyte migration induced by 5 different chemokines, while leaving migration in response to other chemoattractants (such as fMLP or TGF-beta) unaltered. This peptide, and its analogs such as NR58-3.14.3 (i.e. Sequence ID No.1 c(DCys-DGln-DIle-DTrp-DLys-DGln-DLys-DPro-DAsp-DLeu-DCys)-NH<sub>2</sub>),  
30 are collectively termed "Broad Spectrum Chemokine Inhibitors" (BSCIs). Grainger

et al., Biochem. Pharm. 65 (2003) 1027-1034 have subsequently shown BSCIs to have potentially useful anti-inflammatory activity in a range of animal models of diseases. Interestingly, simultaneous blockade of multiple chemokines is not apparently associated with acute or chronic toxicity, suggesting this approach may 5 be a useful strategy for developing new anti-inflammatory medications with similar benefits to steroids but with reduced side-effects.

However, peptides and peptoid derivatives such as NR58-3.14.3, may not be optimal for use in vivo. They are quite expensive to synthesise and have relatively 10 unfavourable pharmacokinetic and pharmacodynamic properties. For example, NR58-3.14.3 is not orally bioavailable and is cleared from blood plasma with a half-life period of less than 30 minutes after intravenous injection.

Two parallel strategies have been adopted to identify novel preparations which 15 retain the anti-inflammatory properties of peptide 3 and NR58-3.14.3, but have improved characteristics for use as pharmaceuticals. Firstly, a series of peptide analogs have been developed, some of which have longer plasma half-lives than NR58-3.14.3 and which are considerably cheaper to synthesise. Secondly, a detailed structure: activity analysis of the peptides has been carried out to identify 20 the key pharmacophores and design small non-peptidic structures which retain the beneficial properties of the original peptide.

This second approach yielded several structurally distinct series of compounds which retained the anti-inflammatory properties of the peptides, including 16-amino 25 and 16-aminoalkyl derivatives of the alkaloid yohimbine, as well as a range of N-substituted 3-aminoglutaramides. (Reference: Fox et al., J Med Chem 45(2002) 360-370; WO 99/12968 and WO 00/42071.) All of these compounds are broad-spectrum chemokine inhibitors which retain selectivity over non-chemokine chemoattractants, and a number of them have been shown to block acute 30 inflammation in vivo.

The most potent and selective of these compounds was (S)-3-(undec-10-enoyl)-aminoglutaramide (NR58,4), which inhibited chemokine-induced migration in vitro with an ED<sub>50</sub> of 5nM. However, further studies revealed that the aminoglutaramide

ring was susceptible to enzymatic ring opening in serum. Consequently, for some applications (for example, where the inflammation under treatment is chronic, such as in autoimmune diseases) these compounds may not have optimal properties, and a more stable compound with similar anti-inflammatory properties may be superior.

5

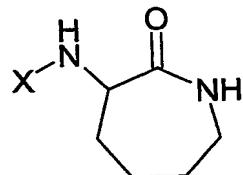
As an approach to identifying such stable analogs, various derivatives of (S)- 3-(undec-10-enoyl)-aminoglutamide have been tested for their stability in serum. One such derivative, the 6-deoxo analog (S)-3-(undec-10-enoyl)-tetrahydropyridin-2-one, is completely stable in human serum for at least 7 days at 37°C, but has  
10 considerably reduced potency compared with the parental molecule.

10

Amide derivatives of 3-aminocaprolactam have already been disclosed in the art. For example:

- Japanese patent application No. 09087331 describes 3-aminocaprolactam amide derivatives wherein the amide alkyl side chain may contain from 2 to 30 carbon atoms. These compounds have been presented as oil-gelating agents.  
15
  - US patent No. 6,395,282 describes immunogenic conjugates comprising a carrier molecule coupled to an autoinducer of a Gram negative bacteria, wherein said autoinducer can be a 3-aminocaprolactam amide derivative wherein the amide alkyl side chain may contain up to 34 carbon atoms. However, a therapeutic use is disclosed only for the conjugates and not for the isolated amide derivative.  
20
  - An article by Weiss et al. (*Research Communications in Psychology, Psychiatry and Behavior* (1992), 17(3-4), 153-159) discloses a series of 3-aminocaprolactam amide derivatives, and among others 3-hexanamido-DL- $\epsilon$ -caprolactam and  
25 3-dodecanamido-DL- $\epsilon$ -caprolactam. These compounds are presented as having only an *in vitro* activity but no significant *in vivo* effect.
- 30 In other words, though some alkyl amide derivatives of 3-aminocaprolactam have certainly been known in the art, no actual pharmaceutical use has been described for 3-aminocaprolactam amide derivatives.

The invention provides the use of a compound of general formula (I), or a pharmaceutically acceptable salt thereof, for the preparation of a medicament intended to treat inflammatory disorder:



(I)

wherein

- 5    X is -CO-R<sup>1</sup> or -SO<sub>2</sub>-R<sup>2</sup>,

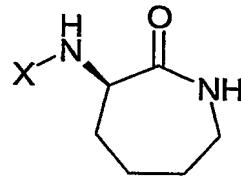
R<sup>1</sup> is an alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl or alkylamino radical of 4 to 20 carbon atoms (for example of 5 to 20 carbon atoms, of 8 to 20 carbon atoms, of 9 to 20 carbon atoms, of 10 to 18 carbon atoms, of 12 to 18 carbon atoms, of 13 to 18 carbon atoms, of 14 to 18 carbon atoms, of 13 to 17 carbon atoms.); and

10      R<sup>2</sup> is an alkyl radical of 4 to 20 carbon atoms (for example of 5 to 20 carbon atoms, of 8 to 20 carbon atoms, of 9 to 20 carbon atoms, of 10 to 18 carbon atoms, of 12 to 18 carbon atoms, of 13 to 18 carbon atoms, of 14 to 18 carbon atoms, and of 13 to 15 carbon atoms).

15      Alternatively R<sup>1</sup> and R<sup>2</sup> may be selected independently from a peptido radical, for example having from 1 to 4 peptidic moieties linked together by peptide bonds (for example a peptido radical of 1 to 4 amino acid residues).

20      The carbon atom at position 3 of the caprolactam ring is asymmetric and consequently, the compounds according to the present invention have two possible enantiomeric forms, that is, the "R" and "S" configurations. The present invention encompasses the two enantiomeric forms and all combinations of these forms, 25 including the racemic "RS" mixtures. With a view to simplicity, when no specific configuration is shown in the structural formulae, it should be understood that the two enantiomeric forms and their mixtures are represented.

Preferably, the compounds of general formula (I) or pharmaceutically acceptable salts thereof used according to this aspect of the invention will be compounds of general formula (I')



(I')

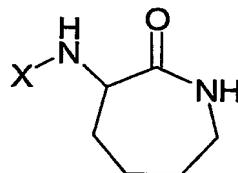
wherein X has the same meaning as above.

5

The compounds of general formula (I) or (I'), or their pharmaceutically acceptable salts, may be such that the alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl or alkylamino part of the R<sup>1</sup> radical is either linear or is branched but contains a linear chain of at least 8 or at least 10 carbon atoms.

10

The invention also provides pharmaceutical compositions comprising, as active ingredient, a compound of general formula (I), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient and/or carrier:



(I)

wherein

15

X is -CO-R<sup>1</sup> or -SO<sub>2</sub>-R<sup>2</sup>,

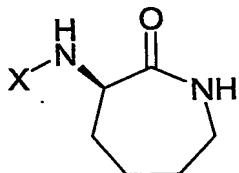
R<sup>1</sup> is an alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl or alkylamino radical of 4 to 20 carbon atoms (for example of 5 to 20 carbon atoms, of 8 to 20 carbon

20 atoms, of 9 to 20 carbon atoms, of 10 to 18 carbon atoms, of 12 to 18 carbon atoms, of 13 to 18 carbon atoms, of 14 to 18 carbon atoms, of 13 to 17 carbon atoms.); and

$R^2$  is an alkyl radical of 4 to 20 carbon atoms (for example of 5 to 20 carbon atoms, of 8 to 20 carbon atoms, of 9 to 20 carbon atoms, of 10 to 18 carbon atoms, of 12 to 18 carbon atoms, of 13 to 18 carbon atoms, of 14 to 18 carbon atoms, and of 13 to 17 carbon atoms).

- 5 Alternatively  $R^1$  and  $R^2$  may be selected independently from a peptido radical, for example having from 1 to 4 peptidic moieties linked together by peptide bonds (for example a peptido radical of 1 to 4 amino acid residues).

Preferably, the compounds of general formula (I) or pharmaceutically acceptable salts thereof used according to this aspect of the invention will be compounds of 10 general formula (I')



(I')

wherein X has the same meaning as above.

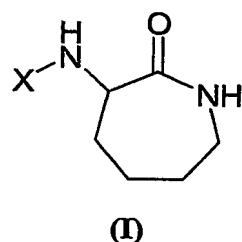
By pharmaceutically acceptable salt is meant in particular the addition salts of 15 inorganic acids such as hydrochloride, hydrobromide, hydroiodide, sulphate, phosphate, diphosphate and nitrate or of organic acids such as acetate, maleate, fumarate, tartrate, succinate, citrate, lactate, methanesulphonate, p-toluenesulphonate, palmoate and stearate. Also within the scope of the present invention, when they can be used, are the salts formed from bases such as sodium 20 or potassium hydroxide. For other examples of pharmaceutically acceptable salts, reference can be made to "Salt selection for basic drugs", *Int. J. Pharm.* (1986), 33, 201-217.

The pharmaceutical composition can be in the form of a solid, for example 25 powders, granules, tablets, gelatin capsules, liposomes or suppositories. Appropriate solid supports can be, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine and wax. Other appropriate

pharmaceutically acceptable excipients and/or carriers will be known to those skilled in the art.

The pharmaceutical compositions according to the invention can also be presented  
5 in liquid form, for example, solutions, emulsions, suspensions or syrups.  
Appropriate liquid supports can be, for example, water, organic solvents such as glycerol or glycols, as well as their mixtures, in varying proportions, in water.

The invention also provides compounds and salts thereof of general formula (I)



10 wherein

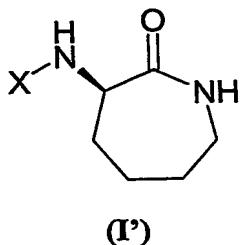
X is -CO-R<sup>1</sup> or -SO<sub>2</sub>-R<sup>2</sup>,

R<sup>1</sup> is an alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl or alkylamino radical  
15 of 4 to 20 carbon atoms (for example of 5 to 20 carbon atoms, of 8 to 20 carbon atoms, of 9 to 20 carbon atoms, of 10 to 18 carbon atoms, of 12 to 18 carbon atoms, of 13 to 18 carbon atoms, of 14 to 18 carbon atoms, of 13 to 17 carbon atoms.); and

R<sup>2</sup> is an alkyl radical of 4 to 20 carbon atoms (for example of 5 to 20 carbon atoms,  
20 of 8 to 20 carbon atoms, of 9 to 20 carbon atoms, of 10 to 18 carbon atoms, of 12 to 18 carbon atoms, of 13 to 18 carbon atoms, of 14 to 18 carbon atoms, and of 13 to 17 carbon atoms).

Alternatively R<sup>1</sup> and R<sup>2</sup> may be selected independently from a peptido radical, for  
25 example having from 1 to 4 peptidic moieties linked together by peptide bonds (for example a peptido radical of 1 to 4 amino acid residues).

Preferably, the compounds of general formula (I) or salts thereof used according to this aspect of the invention will be compounds of general formula (I')



(I')

wherein X has the same meaning as above.

Preferably, the compounds of general formula (I) or (I') when used in the invention, or their salts, will be such that the alkyl, haloalkyl, alkoxy, haloalkoxy, 5 alkenyl, alkynyl or alkylamino part of the R<sup>1</sup> radical is either linear or is branched but contains a linear chain of at least 8 or 10 carbon atoms.

In particular, preferred compounds of general formula (I) or (I') and their salts according to any aspect of the present invention are selected from the group 10 consisting of:

- (S)-3-hexadecanoylamino-caprolactam;
- (S)-3-undecanoylamino-caprolactam;
- (S)-3-(undec-10-enoyl)amino-caprolactam;
- (S)-3-(undec-10-ynoyl)amino-caprolactam;
- (S)-3-tetradecanoylamino-caprolactam;
- (R)-3-hexadecanoylamino-caprolactam;
- (S)-3-octadecanoylamino-caprolactam;
- (S)-(Z)-3-(hexadec-9-enoyl)amino-caprolactam;
- (S)-(Z)-3-(octadec-9-enoyl)amino-caprolactam;
- (R)-(Z)-3-(octadec-9-enoyl)amino-caprolactam;
- (S)-3-(2',2'-dimethyl-dodecanoyl)amino-caprolactam;
- (S)-3-(decyloxycarbonyl)amino-caprolactam;
- (S)-(E)-3-(dodec-2-enoyl)amino-caprolactam;
- (S)-3-(dec-9-enylaminocarbonyl)amino-caprolactam;
- (S)-3-(decylaminocarbonyl)amino-caprolactam;

25 and the salts thereof.

The most preferred compounds will be selected from the group consisting of:  
 (S)-3-hexadecanoylamino-caprolactam (i.e. the compound of general formula (I'))

wherein R<sup>1</sup> is hexadecanyl), (S)-3-(2',2'-dimethyl-dodecanoyl)amino-caprolactam and salts thereof.

- As mentioned in the discussion of prior art above, certain alkyl amide derivatives of 3-amino caprolactam may be known as compounds per se (though it is not presently known that any have been described as such as pharmaceutical compositions or for medical use in an anti-inflammatory context). There may be in the prior art disclosure of straight chain alkyl amide derivatives of 3-amino caprolactam. In so far as any compound is known as such, this compound is not intended to be a compound claimed per se in this invention, and is hereby disclaimed. Consequently the applicant explicitly distinguishes herein between straight chain alkyl derivatives covered by the definition of formula (I) and (I') herein, and branched chain alkyl derivatives of formula (I) and (I') herein. The definition of R<sup>1</sup> used herein in connection with compounds per se may include all alkyl derivatives; alternatively R<sup>1</sup> may include all alkyl derivatives with the exception of certain specified straight chain alkyl derivatives; alternatively R<sup>1</sup> may include all branched chain alkyl derivatives; and as a further alternative the definition of R<sup>1</sup> may exclude all alkyl amide derivatives of 3-amino caprolactam.
- The invention includes compounds, compositions and uses thereof as defined, wherein the compound is in hydrated or solvated form.

As indicated in the Introduction, certain alkyl aminocaprolactam compounds per se, and compositions/conjugates containing them, may already be known in the prior art. Any such known compounds or compositions will be disclaimed from the present invention, either by specific disclaimer or by generic disclaimer of a class of compounds/compositions.

The amide derivatives of 3-aminocaprolactam described here are functional BSCIs. They are relatively inexpensive to synthesise, using facile synthesis routes provided herein; they are stable in human serum and consequently have excellent pharmacokinetic properties; they are orally bioavailable; they are highly potent broad-spectrum chemokine inhibitors in vitro with excellent selectivity over non-chemokine chemoattractants; they are highly potent and effective anti-inflammatory

agents in vivo in rodent models of inflammation; their administration is not associated with any significant acute toxicity at the doses necessary to achieve a maximal therapeutic effect. Taken together, these properties suggest that amide derivatives of 3-aminocaprolactam represent, anti-inflammatory medications with 5 advantages over previously described compounds.

In comparison to the prior art the improvement of the present invention lies in the introduction of the aminocaprolactam moiety. However, the chemical structure of the side chain (whether alkyl amide, alkyl sulfonamide or peptido) can also 10 significantly affect the properties of the molecule, such that alkyl substituents with substitution at the 2-position (relative to the amide carbonyl) or 1-position (relative to the sulfonamide sulfonyl group) are significantly superior to compounds with linear alkyl chains (whether alkyl amides or alkyl sulfonamides).

15 Prior art peptides (such as NR58-3.14.3) have the disadvantages that: (a) they are expensive and require solid phase synthesis (at least for the longer ones) and (b) they clear very quickly via the kidneys and (c) they are generally less potent.

20 The prior art aminoglutarimides are cheap, not cleared quickly via the kidneys and more potent BUT they do not show metabolic stability.

The improvement described here, the aminocaprolactams, are cheap, not cleared by the kidney and even more potent, and are also metabolically stable.

25 According to this invention, inflammatory disorders intended to be prevented or treated by the compounds of general formula (I) or (I') or the pharmaceutically acceptable salts thereof or pharmaceutical compositions or medicaments containing them as active ingredients include notably:

- autoimmune diseases, for example such as multiple sclerosis;
- 30 - vascular disorders including stroke, coronary artery diseases, myocardial infarction, unstable angina pectoris, atherosclerosis or vasculitis, e. g., Behçet's syndrome, giant cell arteritis, polymyalgia rheumatica, Wegener's granulomatosis, Churg-Strauss syndrome vasculitis, Henoch-Schönlein purpura and Kawasaki disease;

- viral infection or replication, e.g. infections due to or replication of viruses including pox virus, herpes virus (e. g., Herpesvirus samiri), cytomegalovirus (CMV) or lentivirus;
  - asthma;
- 5 - osteoporosis; (low bone mineral density);
- tumor growth;
  - rheumatoid arthritis;
  - organ transplant rejection and/or delayed graft or organ function, e.g. in renal transplant patients;
- 10 - a disorder characterised by an elevated TNF- $\alpha$  level;
- psoriasis;
  - skin wounds;
  - disorders caused by intracellular parasites such as malaria or tuberculosis;
  - allergies; or
- 15 - Alzheimer's disease.

According to this invention, further inflammatory disorders include:

- ALS;
- fibrosis (particularly pulmonary fibrosis, but not limited to fibrosis in the lung);

20 - the formation of adhesions (particularly in the peritoneum and pelvic region).

  - antigen induced recall response
  - immune response suppression

These clinical indications fall under the general definition of inflammatory  
25 disorders or disorders characterized by elevated TNF $\alpha$  levels.

Where legally permissible, the invention also provides a method of treatment, amelioration or prophylaxis of the symptoms of an inflammatory disease (including an adverse inflammatory reaction to any agent) by the administration to a patient of  
30 an anti-inflammatory amount of a compound, composition or medicament as claimed herein.

Administration of a medicament according to the invention can be carried out by topical, oral, parenteral route, by intramuscular injection, etc.

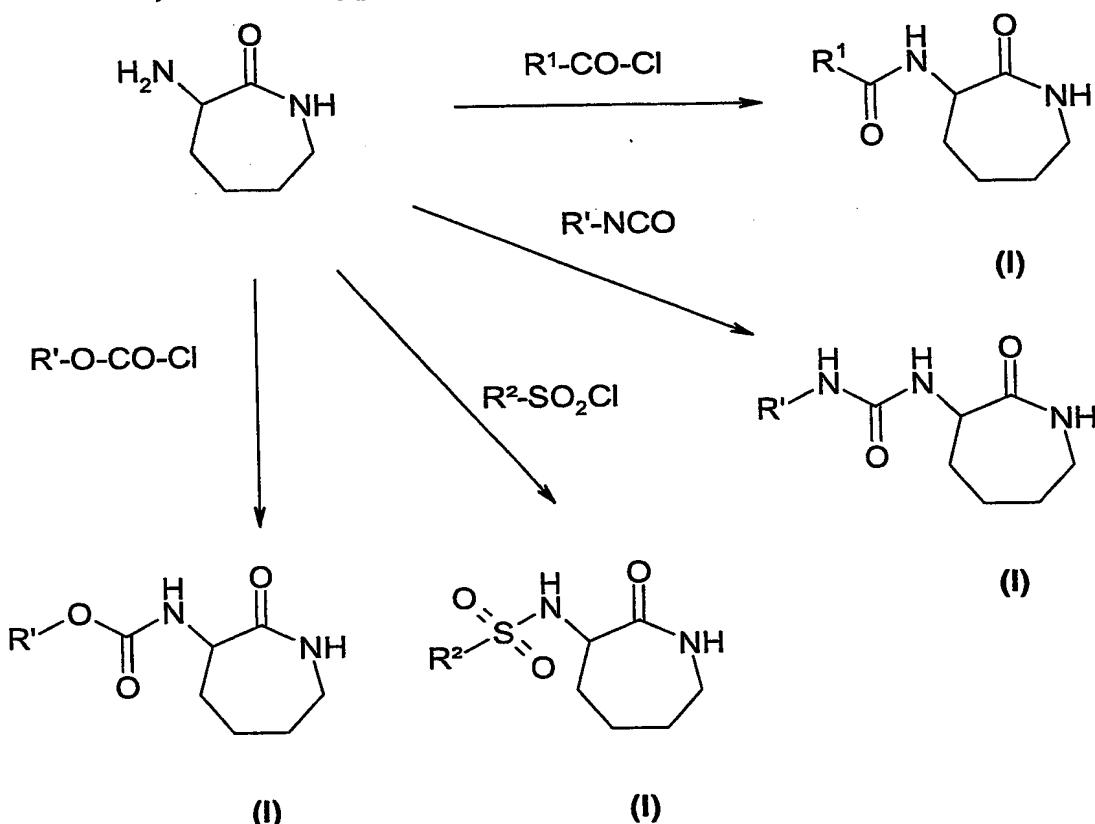
The administration dose envisaged for a medicament according to the invention is comprised between 0.1 mg and 10 g depending on the type of active compound used.

- According to the invention, the compounds of general formula (I) or (I') can be  
5 prepared using the processes described hereafter.

**Preparation of the compounds of general formula (I) or (I')**

- All the compounds of general formula (I') or (I'') can be prepared easily according  
10 to general methods known to the person skilled in the art.

Nevertheless, the following preferred synthetic routes are proposed:



**Diagram 1**

According to the routes shown in Diagram 1:

- ❖ 3-amino-caprolactam is treated by an acid chloride of general formula  $R^1\text{-CO-Cl}$  wherein  $R^1$  is an alkyl, haloalkyl, alkenyl or alkynyl radical to produce the  
15

- compounds of general formula (I) wherein X is  $-CO-R^1$  and R<sup>1</sup> is an alkyl, haloalkyl, alkenyl or alkynyl radical; or
- ❖ 3-amino-caprolactam is treated by an isocyanate of general formula R'-NCO wherein R' is alkyl to produce the compounds of general formula (I) wherein X is  $-CO-R^1$  and R<sup>1</sup> is an alkylamino radical ;
  - ❖ 3-amino-caprolactam is treated by a sulphonylchloride of general formula R<sup>2</sup>-SO<sub>2</sub>Cl wherein R<sup>2</sup> is alkyl to produce the compounds of general formula (I) wherein X is  $-SO_2-R^2$  and R<sup>2</sup> is an alkyl radical ; or
  - ❖ 3-amino-caprolactam is treated by a chloroformate of general formula R'-O-CO-Cl wherein R' is alkyl to produce the compounds of general formula (I) wherein X is  $-CO-R^1$  and R<sup>1</sup> is an alkoxy radical.

The reactions shown in Diagram 1 may be carried out, for example, in chloroform or dichloromethane. The most preferred reaction solvent is dichloromethane. The above reactions are preferably carried out in the presence of a base, for example Na<sub>2</sub>CO<sub>3</sub>.

All the above reactions may be carried out at ambient temperature (about 25 °C) or more generally at a temperature between 20 and 50 °C.

### DEFINITIONS

The term "about" refers to an interval around the considered value. As used in this patent application, "about X" means an interval from X minus 10% of X to X plus 10% of X, and preferably an interval from X minus 5% of X to X plus 5% of X.

The use of a numerical range in this description is intended unambiguously to include within the scope of the invention all individual integers within the range and all the combinations of upper and lower limit numbers within the broadest scope of the given range. Hence, for example, the range of 4 to 20 carbon atoms specified in respect of (*inter alia*) formula I is intended to include all integers between 4 and 20 and all sub-ranges of each combination of upper and lower numbers, whether exemplified explicitly or not.

As used herein, the term "comprising" is to be read as meaning both comprising and consisting of. Consequently, where the invention relates to a "pharmaceutical composition comprising as active ingredient" a compound, this terminology is  
5 intended to cover both compositions in which other active ingredients may be present and also compositions which consist only of one active ingredient as defined.

The term "peptidic moieties" used herein is intended to include the following 20 naturally-occurring proteogenic amino acid residues:

SYMBOL	MEANING
Ala	Alanine
Cys	Cysteine
Asp	Aspartic Acid
Glu	Glutamic Acid
Phe	Phenylalanine
Gly	Glycine
His	Histidine
Ile	Isoleucine
Lys	Lysine
Leu	Leucine
Met	Methionine
Asn	Asparagine
Pro	Proline
Gln	Glutamine
Arg	Arginine
Ser	Serine
Thr	Threonine
Val	Valine
Trp	Tryptophan
Tyr	Tyrosine

Modified and unusual amino acid residues, as well as peptido-mimetics, are also intended to be encompassed within the definition of "peptidic moieties".

- 5 Unless otherwise defined, all the technical and scientific terms used here have the same meaning as that usually understood by an ordinary specialist in the field to which this invention belongs. Similarly, all the publications, patent applications, all the patents and all other references mentioned here are incorporated by way of reference (where legally permissible).

10

The following examples are presented in order to illustrate the above procedures and should in no way be considered to limit the scope of the invention.

## **FIGURES**

Figure 1 provides a comparison of (R)-and (S)- enantiomers of amide derivatives of aminocaprolactam as inhibitors of MCP-1 induced migration.

## **EXAMPLES**

15

### *General procedure for the synthesis of the starting compounds*

The hydrochlorides of (R) and (S)-3-amino-caprolactam, and the hydro-pyrrolidine-5-carboxylates of (R,R) and (S,S)-3-amino-caprolactam were synthesised according  
20 to literature (cf. Boyle et al., *J. Am. Chem. Soc.* (1979), 44, 4841-4847; Rezler et al., *J. Med. Chem.* (1997), 40, 3508-3515).

### **Example 1: (S)-3-hexadecanoylamino-caprolactam:**

(S)-3-amino-caprolactam hydrochloride 1 (5 mmol) and Na<sub>2</sub>CO<sub>3</sub> (15 mmol) in  
25 water (25 ml) were added to a solution of hexadecanoyl chloride (5 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic

layers were dried over  $\text{Na}_2\text{CO}_3$  and reduced *in vacuo*. The residue was purified by recrystallisation from EtOAc to give the title compound (1.41 g; 77%).

Melting point: 99-100 °C.

$[\alpha]_D^{25}$  ( $c = 1, \text{CHCl}_3$ ) = +32.0.

- 5 IR:  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3325, 3272 (NH), 1666, 1655, 1631 (CO), 1524 (NH).  
 $^1\text{H}$  NMR ( $\delta_H$ , 500 MHz,  $\text{CDCl}_3$ ): 6.88 (1H, d,  $J$  5.5,  $\text{CHNH}$ ), 6.72 (1H, br s,  $\text{CH}_2\text{NH}$ ), 4.49 (1H, ddd,  $J$  11, 6, 1,  $\text{CHNH}$ ), 3.29-3.16 (2H, m,  $\text{CH}_2\text{NH}$ ), 2.17 (2H, t,  $J$  7.5,  $\text{CH}_2\text{CONH}$ ), 2.03 (1H, br d,  $J$  13.5, ring CH), 1.98-1.89 (1H, m, ring CH), 1.85-1.73 (2H, m, ring CH), 1.58 (2H, br qn  $J$  7.0,  $\text{CH}_2\text{CH}_2\text{CONH}$ ), 1.43 (1H, br qd,  
10 14, 3, ring CH), 1.38-1.29 (1H, br m, ring CH), 1.29-1.14 (24H, m,  $(\text{CH}_2)_{12}$ ) and 0.83 (3H, t,  $J$  6.5,  $\text{CH}_3$ ).  
 $^{13}\text{C}$  NMR ( $\delta_C$ , 125 MHz,  $\text{CDCl}_3$ ): 175.9, 172.3 (CO), 52.0 (NHCHCO), 42.1 (NCH<sub>2</sub>), 36.6, 31.9, 31.7, 29.6 ( $\times 6$ ), 29.4, 29.3 ( $\times 2$ ), 29.2, 28.8, 27.9, 25.6, 22.6  
15 ( $\text{CH}_2$ ) and 14.1 ( $\text{CH}_3$ ).  
m/z ( $\text{C}_{22}\text{H}_{42}\text{N}_2\text{O}_2\text{Na}$ ): 389.31450 (calculated: 389.3144).

**Example 2: (S)-3-undecanoylamino-caprolactam:**

- 20 (S)-3-amino-caprolactam hydrochloride (2 mmol) and  $\text{Na}_2\text{CO}_3$  (6 mmol) in water (25 ml) were added to a solution of undecanoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic  
25 layers were dried over  $\text{Na}_2\text{CO}_3$  and reduced *in vacuo*. The residue was purified by recrystallisation from EtOAc to give the title compound (397 mg, 67%).

Melting point: 91-92 °C.

$[\alpha]_D^{25}$  ( $c = 1, \text{CHCl}_3$ ) = +30.2.

- IR:  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3342, 3313 (NH), 1676, 1638 (CO), 1519 (NH); 3342, 3292 (NH), 1671, 1639 (CO), 1513 (NH).  
 $^1\text{H}$  NMR ( $\delta_H$ , 500 MHz,  $d_6\text{-DMSO}$ ): 7.76 (1H, t,  $J$  6,  $\text{CH}_2\text{NH}$ ), 7.68 (1H, d,  $J$  7,  $\text{CHNH}$ ), 4.38 (1H, dd,  $J$  10, 7,  $\text{CHNH}$ ), 3.15 (1H, ddd,  $J$  15.5, 11, 5,  $\text{CHHNH}$ ), 3.04 (1H, dt,  $J$  13, 6,  $\text{CHHNH}$ ), 2.19-2.06 (2H, m,  $\text{CH}_2\text{CONH}$ ), 1.85 (1H, dt,  $J$  10.5, 3, C-5 H), 1.77-1.68 (2H, m, C-4 H, C-6 H), 1.60 (1H, qt,  $J$  12, 3.5, C-5 H), 1.46

(2H, br qn  $J$  6.5,  $\text{CH}_2\text{CH}_2\text{CONH}$ ), 1.35 (1H, qd,  $J$  12.5, 3, C-4 H), 1.31-1.13 (15H, m,  $(\text{CH}_2)_7$  + C-6 H) and 0.85 (3H, t,  $J$  7.0,  $\text{CH}_3$ ).

$^{13}\text{C}$  NMR ( $\delta_{\text{C}}$ , 125 MHz,  $d_6$ -DMSO): 174.4 (CO-ring), 171.3 (CO-chain), 51.3 (NHCHCO), 40.7 (NCH<sub>2</sub>), 35.2, 31.4, 31.3, 29.1, 29.0 ( $\times 2$ ), 28.9, 28.8, 28.7,

5 27.8, 25.4, 22.2 ( $\text{CH}_2$ ) and 14.0 ( $\text{CH}_3$ ).

m/z ( $\text{C}_{17}\text{H}_{32}\text{N}_2\text{O}_2\text{Na}$ ): 319.23540 (calculated: 319.2361).

**Example 3: (S)-3-(undec-10-enoyl)amino-caprolactam:**

10 (S)-3-amino-caprolactam hydrochloride (2 mmol) and  $\text{Na}_2\text{CO}_3$  (6 mmol) in water (25 ml) were added to a solution of undec-10-enoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane ( $2 \times 25$  ml). The combined organic  
15 layers were dried over  $\text{Na}_2\text{CO}_3$  and reduced *in vacuo*. The residue was purified by recrystallisation from EtOAc to give the title compound (423 mg; 72%).

Melting point: 83-84 °C.

$[\alpha]_D^{25}$  ( $c = 1$ ,  $\text{CHCl}_3$ ) = +40.1.

IR:  $\nu_{\text{max}}$  (cm<sup>-1</sup>): 3327, 3273 (NH), 1655, 1630 (CO), 1521 (NH).

20  $^1\text{H}$  NMR ( $\delta_{\text{H}}$ , 500 MHz,  $d_6$ -DMSO): 7.75 (1H, t,  $J$  6,  $\text{CH}_2\text{NH}$ ), 7.66 (1H, d,  $J$  7,  $\text{CHNH}$ ), 5.76 (1H, ddt,  $J$  17, 10, 6.5  $\text{CH}_2=\text{CH}$ ), 4.96 (1H, dq,  $J$  17, 2,  $\text{CHH}=\text{CH}$ ), 4.96 (1H, ddt,  $J$  17, 2, 1,  $\text{CHH}=\text{CH}$ ), 4.36 (1H, dd,  $J$  10, 7,  $\text{CHNH}$ ), 3.14 (1H, ddd,  $J$  15.5, 11.5, 5,  $\text{CHHNH}$ ), 3.03 (1H, br dt,  $J$  13, 5.5,  $\text{CHHNH}$ ), 2.16-2.06 (2H, m,  $\text{CH}_2\text{CONH}$ ), 1.98 (2H, br q,  $J$  7,  $\text{CH}_2=\text{CHCH}_2$ ), 1.85 (1H, dt,  $J$  10.5, 3, C-5 H),  
25 1.75-1.67 (2H, m, C-4 H, C-6 H), 1.60 (1H, qt,  $J$  13, 3.5, C-5 H), 1.44 (2H, br qn,  $J$  7,  $\text{CH}_2\text{CH}_2\text{CONH}$ ), 1.39-1.27 (3H, m,  $\text{CH}_2=\text{CHCH}_2\text{CH}_2$  + C-4 H) and 1.31-1.13 (9H, m,  $(\text{CH}_2)_4$  + C-6 H).

$^{13}\text{C}$  NMR ( $\delta_{\text{C}}$ , 125 MHz,  $d_6$ -DMSO): 174.4 (CO-ring), 171.3 (CO-chain),

138.9 ( $\text{CH}_2=\text{CH}$ ), 114.7 ( $\text{CH}_2=\text{CH}$ ), 51.3 (NHCHCO), 40.7 (NCH<sub>2</sub>), 35.3, 33.3,

30 31.3, 29.0, 28.9 ( $\times 2$ ) 28.7, 28.6, 28.4, 27.8 and 25.4 ( $\text{CH}_2$ ).

m/z ( $\text{C}_{17}\text{H}_{30}\text{N}_2\text{O}_2\text{Na}$ ): 317.21970 (calculated: 317.2205).

**Example 4: (S)-3-(undec-10-ynoyl)amino-caprolactam:**

(S)-3-amino-caprolactam hydrochloride (2 mmol) and  $\text{Na}_2\text{CO}_3$  (6 mmol) in water (25 ml) were added to a solution of undec-10-ynoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane ( $2 \times 25$  ml). The combined organic layers were dried over  $\text{Na}_2\text{CO}_3$  and reduced *in vacuo*. The residue was purified by recrystallisation from EtOAc to give the title compound (362 mg; 62%).

5 Melting point: 73-75 °C.

$[\alpha]_D^{25}$  ( $c = 1, \text{CHCl}_3$ ) = +42.1.

- 10 IR:  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3332, 3295 (NH), 1667, 1633 (CO), 1523 (NH).  
 $^1\text{H}$  NMR ( $\delta_{\text{H}}$ , 500 MHz,  $d_6$ -DMSO): 7.76 (1H, t,  $J$  5.5,  $\text{CH}_2\text{NH}$ ), 7.68 (1H, d,  $J$  7,  $\text{CHNH}$ ), 4.36 (1H, dd,  $J$  11, 7,  $\text{CHNH}$ ), 3.16 (1H, ddd,  $J$  15.5, 11.5, 5,  $\text{CHHNH}$ ), 3.03 (1H, br dt,  $J$  14, 7,  $\text{CHHNH}$ ), 2.17-2.07 (4H, m,  $\text{CH}_2\text{CONH} + \text{CH}_2\text{CCH}$ ), 1.85 (1H, m, C-5 H), 1.77-1.67 (2H, m, C-4 H, C-6 H), 1.62 (1H, br qt,  $J$  13, 3.0, C-5 H), 1.50-1.28 (5H, m,  $\text{CH}_2\text{CH}_2\text{CONH} + \text{HCCCH}_2\text{CH}_2 + \text{C-4 H}$ ) and 1.28-1.13 (9H, m,  $(\text{CH}_2)_4 + \text{C-6 H}$ ).  
 $^{13}\text{C}$  NMR ( $\delta_{\text{C}}$ , 125 MHz,  $d_6$ -DMSO): 174.4 (CO-ring), 171.3 (CO-chain), 84.6 ( $\text{CH}_2\text{CCH}$ ), 71.1 ( $\text{CH}_2\text{CCH}$ ), 51.3 (NHCHCO), 40.7 (NCH<sub>2</sub>), 35.2, 31.3, 29.0, 28.8, 28.7, 28.5, 28.2, 28.0, 27.8, 25.4 and 17.8 (CH<sub>2</sub>).  
20 m/z ( $\text{C}_{17}\text{H}_{28}\text{N}_2\text{O}_2\text{Na}$ ): 317.20470 (calculated: 315.2048).

**Example 5: (S)-3-dodecanoylamino-caprolactam:**

(S)-3-amino-caprolactam hydrochloride (2 mmol) and  $\text{Na}_2\text{CO}_3$  (6 mmol) in water (25 ml) were added to a solution of dodecanoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane ( $2 \times 25$  ml). The combined organic layers were dried over  $\text{Na}_2\text{CO}_3$  and reduced *in vacuo*. The residue was purified by recrystallisation from EtOAc to give the title compound (439 mg, 71%).

30 Melting point: 93-94 °C.

$[\alpha]_D^{25}$  ( $c = 1, \text{CHCl}_3$ ) = +35.5.

IR:  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3324, 3267 (NH), 1666, 1630 (CO), 1521 (NH).

$^1\text{H}$  NMR ( $\delta_{\text{H}}$ , 500 MHz,  $d_6$ -DMSO): 7.76 (1H, br s,  $\text{CH}_2\text{NH}$ ), 7.67 (1H, d,  $J$  7,  $\text{CHNH}$ ), 4.38 (1H, dd,  $J$  10.5, 7.5,  $\text{CHNH}$ ), 3.15 (1H, ddd,  $J$  15.5, 11.5, 5,

*CHHNH), 3.05 (1H, dt, *J* 14.5, 5.5, CHHNH), 2.17-2.07 (2H, m, CH<sub>2</sub>CONH), 1.90-1.80 (1H, m, C-5 H), 1.77-1.68 (2H, m, C-4 H, C-6 H), 1.62 (1H, br qt, *J* 12, 3.5, C-5 H), 1.46 (2H, br qn *J* 6.0, CH<sub>2</sub>CH<sub>2</sub>CONH), 1.36 (1H, qd, *J* 12.5, 2.5, C-4 H), 1.31-1.13 (17H, m, (CH<sub>2</sub>)<sub>8</sub> + C-6 H) and 0.85 (3H, t, *J* 6.5, CH<sub>3</sub>).*

5 <sup>13</sup>C NMR ( $\delta_{\text{C}}$ , 125 MHz, d<sub>6</sub>-DMSO): 174.4 (CO-ring), 171.2 (CO-chain), 51.3 (NHCHCO), 40.7 (NCH<sub>2</sub>), 35.3, 31.4, 31.3, 29.1 ( $\times 3$ ), 29.0 ( $\times 2$ ), 28.8, 28.7, 27.8, 25.4, 22.2 (CH<sub>2</sub>) and 14.0 (CH<sub>3</sub>).  
m/z (C<sub>18</sub>H<sub>34</sub>N<sub>2</sub>O<sub>2</sub>Na): 333.25150 (calculated: 333.2518).

10 **Example 6: (S)-3-tetradecanoylamino-caprolactam:**

(S)-3-amino-caprolactam hydrochloride (2 mmol) and Na<sub>2</sub>CO<sub>3</sub> (6 mmol) in water (25 ml) were added to a solution of tetradecanoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2  $\times$  25 ml). The combined organic layers were dried over Na<sub>2</sub>CO<sub>3</sub> and reduced *in vacuo*. The residue was purified by recrystallisation from EtOAc to give the title compound (412 mg; 61%).

Melting point: 97-98 °C.

[ $\alpha$ ]<sub>D</sub><sup>25</sup> (c = 1, CHCl<sub>3</sub>) = +33.2.

20 IR:  $\nu_{\text{max}}$  (cm<sup>-1</sup>): 3326, 3273 (NH), 1666, 1655, 1631 (CO), 1523 (NH).

<sup>1</sup>H NMR ( $\delta_{\text{H}}$ , 500 MHz, CDCl<sub>3</sub>): 6.87 (1H, d, *J* 5.5, CHNH), 6.66-6.48 (1H, br m, CH<sub>2</sub>NH), 4.50 (1H, dd, *J* 11, 6, CHNH), 3.30-3.16 (2H, m, CH<sub>2</sub>NH), 2.18 (2H, t, *J* 7.5, CH<sub>2</sub>CONH), 2.04 (1H, br d, *J* 13.5, ring CH), 2.00-1.92 (1H, m, ring CH), 1.86-1.74 (2H, m, ring CH), 1.59 (2H, br qn *J* 7.0, CH<sub>2</sub>CH<sub>2</sub>CONH), 1.43 (1H, br q, *J* 12.5, ring CH), 1.31 (1H, br q, *J* 13, ring CH), 1.31-1.13 (20H, m, (CH<sub>2</sub>)<sub>10</sub>) and 0.85 (3H, t, *J* 6.5, CH<sub>3</sub>).

<sup>13</sup>C NMR ( $\delta_{\text{C}}$ , 125 MHz, CDCl<sub>3</sub>): 175.9, 172.3 (CO), 52.0 (NHCHCO), 42.1 (NCH<sub>2</sub>), 36.6, 31.9, 31.7, 29.6 ( $\times 4$ ), 29.4, 29.3 ( $\times 2$ ), 29.2, 28.8, 27.9, 25.6, 22.6 (CH<sub>2</sub>) and

30 14.1 (CH<sub>3</sub>).

m/z (C<sub>20</sub>H<sub>38</sub>N<sub>2</sub>O<sub>2</sub>Na): 361.28270 (calculated: 361.2831).

**Example 7: (R)-3-hexadecanoylamino-caprolactam:**

(*R,R*)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (5 mmol) and Na<sub>2</sub>CO<sub>3</sub> (15 mmol) in water (25 ml) were added to a solution of hexadecanoyl chloride (5 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na<sub>2</sub>CO<sub>3</sub> and reduced *in vacuo*. The residue was purified by recrystallisation from EtOAc to give the title compound (1.23 g; 67%).

Melting point: 99-100 °C.

[ $\alpha$ ]<sub>D</sub><sup>25</sup> (c = 1, CHCl<sub>3</sub>) = -32.0.

10

**Example 8: (*S*)-3-octadecanoylamino-caprolactam:**

(*S*)-3-amino-caprolactam hydrochloride (2 mmol) and Na<sub>2</sub>CO<sub>3</sub> (6 mmol) in water (25 ml) were added to a solution of octadecanoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na<sub>2</sub>CO<sub>3</sub> and reduced *in vacuo*. The residue was purified by recrystallisation from EtOAc to give the title compound (648 mg; 82%).

Melting point: 87-88 °C.

20 [ $\alpha$ ]<sub>D</sub><sup>25</sup> (c = 1, CHCl<sub>3</sub>) = +31.9.

IR:  $\nu_{\text{max}}$  (cm<sup>-1</sup>): 3327, 3272 (NH), 1667, 1655, 1631 (CO), 1524 (NH).

<sup>1</sup>H NMR ( $\delta_{\text{H}}$ , 500 MHz, CDCl<sub>3</sub>): 6.88 (1H, d, *J* 5.5, CHNH), 6.72-6.58 (1H, br m, CH<sub>2</sub>NH), 4.50 (1H, dd, *J* 11, 6, CHNH), 3.29-3.16 (2H, m, CH<sub>2</sub>NH), 2.17 (2H, t, *J* 7.5, CH<sub>2</sub>CONH), 2.03 (1H, br d, *J* 13, ring CH), 1.99-1.90 (1H, m, ring CH), 1.86-25 1.73 (2H, m, ring CH), 1.58 (2H, br qn *J* 7.0, CH<sub>2</sub>CH<sub>2</sub>CONH), 1.42 (1H, br qd, *J* 14, 3, ring CH), 1.38-1.30 (1H, br m, ring CH), 1.30-1.14 (28H, m, (CH<sub>2</sub>)<sub>14</sub>) and 0.84 (3H, t, *J* 6.5, CH<sub>3</sub>).

<sup>13</sup>C NMR ( $\delta_{\text{C}}$ , 125 MHz, CDCl<sub>3</sub>): 175.9, 172.3 (CO), 52.0 (NHCHCO), 42.1 (NCH<sub>2</sub>), 36.6, 31.9, 31.7, 29.6 ( $\times 8$ ), 29.4, 29.3 ( $\times 2$ ), 29.2, 28.8, 27.9, 25.6, 22.6 (CH<sub>2</sub>) and 30 14.1 (CH<sub>3</sub>).

m/z (C<sub>24</sub>H<sub>46</sub>N<sub>2</sub>O<sub>2</sub>Na): 417.34460 (calculated: 417.3457).

**Example 9: (S)-(Z)-3-(hexadec-9-enoyl)amino-caprolactam:**

(*S,S*)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate **2** (2 mmol) and

- 5  $\text{Na}_2\text{CO}_3$  (6 mmol) in water (25 ml) were added to a solution of (*Z*)-hexadec-9-enoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane ( $2 \times 25$  ml). The combined organic layers were dried over  $\text{Na}_2\text{CO}_3$  and reduced *in vacuo*. The residue  
10 was purified by silica column chromatography (eluent: EtOAc to 9:1 EtOAc:MeOH) to give the title compound (406 mg; 56%).

Melting point: 67-68 °C.

$[\alpha]_D^{25}$  ( $c = 1$ ,  $\text{CHCl}_3$ ) = +33.2.

IR:  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3324, 3268 (NH), 1655, 1630 (CO), 1524 (NH).

- 15  $^1\text{H}$  NMR ( $\delta_{\text{H}}$ , 500 MHz,  $\text{CDCl}_3$ ): 6.88 (1H, d,  $J$  5.5,  $\text{CHNH}$ ), 6.67 (1H, br s,  $\text{CH}_2\text{NH}$ ), 5.33-5.25 (2H, m,  $\text{CH}=\text{CH}$ ), 4.50 (1H, ddd,  $J$  11, 6, 1,  $\text{CHNH}$ ), 3.29-3.16 (2H, m,  $\text{CH}_2\text{NH}$ ), 2.17 (2H, t,  $J$  7.5,  $\text{CH}_2\text{CONH}$ ), 2.03 (1H, br d,  $J$  13, ring CH), 1.99-1.90 (5H, m, ring CH +  $\text{CH}_2\text{CH}=\text{CHCH}_2$ ), 1.84-1.72 (2H, m, ring CH), 1.58 (2H, br qn  $J$  7.0,  $\text{CH}_2\text{CH}_2\text{CONH}$ ), 1.43 (1H, br qd,  $J$  14, 3, ring CH), 1.38-1.30 (1H, 20 br m, ring CH), 1.30-1.14 (16H, m,  $(\text{CH}_2)_4\text{CH}_2\text{CH}=\text{CHCH}_2(\text{CH}_2)_4$ ) and 0.84 (3H, t,  $J$  7,  $\text{CH}_3$ ).

$^{13}\text{C}$  NMR ( $\delta_{\text{C}}$ , 125 MHz,  $\text{CDCl}_3$ ): 175.9, 172.3 (CO), 129.8 ( $\times 2$ ) ( $\text{CH}=\text{CH}$ ), 52.0 (NHCHCO), 42.0 (NCH<sub>2</sub>), 36.6, 31.7 ( $\times 2$ ), 29.7 ( $\times 2$ ), 29.2 ( $\times 2$ ), 29.1, 29.0, 28.8, 27.9, 27.2, 27.1, 25.6, 22.6 ( $\text{CH}_2$ ) and 14.1 ( $\text{CH}_3$ ).

- 25 m/z ( $\text{C}_{22}\text{H}_{40}\text{N}_2\text{O}_2\text{Na}$ ): 387.29700 (calculated: 387.2987).

**Example 10: (S)-(Z)-3-(octadec-9-enoyl)amino-caprolactam:**

(*S,S*)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (2 mmol) and  $\text{Na}_2\text{CO}_3$

- 30 (6 mmol) in water (25 ml) were added to a solution of (*Z*)-octadec-9-enoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane ( $2 \times 25$  ml). The combined organic layers were dried over  $\text{Na}_2\text{CO}_3$  and reduced *in vacuo*. The residue

was purified by silica column chromatography (eluent: EtOAc to 9:1 EtOAc:MeOH) to give the title compound (514 mg; 66%).

Melting point: 66-67 °C.

$[\alpha]_D^{25}$  ( $c = 1$ , CHCl<sub>3</sub>) = +30.9.

- 5 IR:  $\nu_{\text{max}}$  (cm<sup>-1</sup>): 3327, 3268 (NH), 1655, 1631 (CO), 1523 (NH).  
<sup>1</sup>H NMR ( $\delta_H$ , 500 MHz, CDCl<sub>3</sub>): 6.88 (1H, d,  $J$  5.5, CHNH), 6.74 (1H, br t,  $J$  5, CH<sub>2</sub>NH), 5.33-5.24 (2H, m, CH=CH), 4.49 (1H, ddd,  $J$  11, 6, 1.5, CHNH), 3.29-3.14 (2H, m, CH<sub>2</sub>NH), 2.16 (2H, t,  $J$  7.5, CH<sub>2</sub>CONH), 2.03 (1H, br d,  $J$  13.5, ring CH), 1.99-1.89 (5H, m, ring CH + CH<sub>2</sub>CH=CHCH<sub>2</sub>), 1.84-1.72 (2H, m, ring CH),  
10 1.58 (2H, br qn  $J$  7.0, CH<sub>2</sub>CH<sub>2</sub>CONH), 1.42 (1H, br qd,  $J$  14, 3, ring CH), 1.38-1.30 (1H, br m, ring CH), 1.30-1.14 (20H, m, (CH<sub>2</sub>)<sub>6</sub>CH<sub>2</sub>CH=CHCH<sub>2</sub>(CH<sub>2</sub>)<sub>4</sub>) and 0.83 (3H, t,  $J$  7, CH<sub>3</sub>).  
<sup>13</sup>C NMR ( $\delta_C$ , 125 MHz, CDCl<sub>3</sub>): 175.9, 172.3 (CO), 129.9, 129.7 (CH=CH), 52.0 (NHCHCO), 42.0 (NCH<sub>2</sub>), 36.6, 31.8, 31.7, 29.7 ( $\times 2$ ), 29.5, 29.3 ( $\times 3$ ), 29.2, 29.1, 28.8, 27.9, 27.2, 27.1, 25.6, 22.6 (CH<sub>2</sub>) and 14.1 (CH<sub>3</sub>).  
m/z (C<sub>24</sub>H<sub>44</sub>N<sub>2</sub>O<sub>2</sub>Na): 415.32820 (calculated: 415.3300).

**Example 11: (R)-(Z)-3-(octadec-9-enoyl)amino-caprolactam:**

- 20 (R,R)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate 2 (2 mmol) and Na<sub>2</sub>CO<sub>3</sub> (6 mmol) in water (25 ml) were added to a solution of (Z)-octadec-9-enoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na<sub>2</sub>CO<sub>3</sub> and reduced *in vacuo*. The residue was purified by silica column chromatography (eluent: EtOAc to 9:1 EtOAc:MeOH) to give the title compound (574 mg; 73%).

Melting point: 66-67 °C.

$[\alpha]_D^{25}$  ( $c = 1$ , CHCl<sub>3</sub>) = -31.4.

30

**Example 12: (S)-3-(2',2'-dimethyl-dodecanoyl)amino-caprolactam:**

(S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate 2 (2 mmol) and Na<sub>2</sub>CO<sub>3</sub> (6 mmol) in water (25 ml) were added to a solution of 2,2-dimethyl-dodecanoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature

and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane ( $2 \times 25$  ml). The combined organic layers were dried over  $\text{Na}_2\text{CO}_3$  and reduced *in vacuo*. The residue was purified by silica column chromatography (eluent: EtOAc to 9:1 EtOAc:MeOH) to give the title compound (543 mg; 80%).

Melting point: 41-42 °C.

$[\alpha]_D^{25}$  ( $c = 1, \text{CHCl}_3$ ) = +28.0.

IR:  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3403, 3265 (NH), 1673, 1641 (CO), 1497 (NH).

$^1\text{H}$  NMR ( $\delta_{\text{H}}, 500$  MHz,  $\text{CDCl}_3$ ): 7.08 (1H, d,  $J 5.5, \text{CHNH}$ ), 6.67 (1H, br s,

10  $\text{CH}_2\text{NH}$ ), 4.44 (1H, dd,  $J 11, 5.5, \text{CHNH}$ ), 3.28-3.15 (2H, m,  $\text{CH}_2\text{NH}$ ), 2.01 (1H, br d,  $J 13$ , ring CH), 1.98-1.89 (1H, m, ring CH), 1.84-1.72 (2H, m, ring CH), 1.47-1.30 (3H, br m, ring CH +  $\text{CH}_2\text{CMe}_2\text{CONH}$ ), 1.27-1.15 (17H, br m, ring CH +  
( $\text{CH}_2$ )<sub>8</sub>) 1.13 (3H, s, CMeMe), 1.12 (3H, s, CMeMe) and 0.82 (3H, t,  $J 7, \text{CH}_2\text{CH}_3$ ).

15  $^{13}\text{C}$  NMR ( $\delta_{\text{C}}, 125$  MHz,  $\text{CDCl}_3$ ): 177.1, 176.0 (CO), 52.0 (NHCHCO), 41.9

(CMe<sub>2</sub>), 42.1, 41.3, 31.8, 31.5, 30.1, 29.6, 29.5 ( $\times 2$ ), 29.3, 28.9, 27.9 ( $\text{CH}_2$ ), 25.3, 25.2 ( $\text{CH}_3$ ), 24.8, 22.6 ( $\text{CH}_2$ ) and 14.1 ( $\text{CH}_3$ ).

m/z ( $\text{C}_{20}\text{H}_{38}\text{N}_2\text{O}_2\text{Na}$ ): 361.28350 (calculated: 361.2831).

20 **Example 13: (S)-3-(decyloxycarbonyl)amino-caprolactam:**

(*S,S*)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (2 mmol) and  $\text{Na}_2\text{CO}_3$  (6 mmol) in water (25 ml) were added to a solution of decyl chloroformate (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase

25 was extracted with additional dichloromethane ( $2 \times 25$  ml). The combined organic layers were dried over  $\text{Na}_2\text{CO}_3$  and reduced *in vacuo*. The residue was purified by silica column chromatography (eluent: EtOAc to 9:1 EtOAc:MeOH) to give the title compound (459 mg; 74%).

Melting point: 40-41 °C.

30  $[\alpha]_D^{25}$  ( $c = 1, \text{CHCl}_3$ ) = +31.4.

IR:  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3352, 3300 (NH), 1682, 1657, 1637 (CO), 1513 (NH).

$^1\text{H}$  NMR ( $\delta_{\text{H}}, 500$  MHz,  $\text{CDCl}_3$ ): 6.86 (1H, br s,  $\text{CH}_2\text{NH}$ ), 6.72 (1H, d,  $J 6 \text{ CHNH}$ ),

4.49 (1H, dd,  $J 11, 6, \text{CHNH}$ ), 3.99 (2H, t,  $J 6, \text{OCH}_2$ ), 3.26-3.14 (2H, m,  $\text{CH}_2\text{NH}$ ),

2.04 (1H, br d,  $J 13.5$ , ring CH), 2.00-1.91 (1H, m, ring CH), 1.82-1.68 (2H, m, ring

CH), 1.55 (2H, br qn  $J$  7.0,  $\text{CH}_2\text{CH}_2\text{O}$ ), 1.48 (1H, br qd,  $J$  14, 2.5, ring CH), 1.38-1.31 (1H, br m, ring CH), 1.29-1.17 (14H, m,  $(\text{CH}_2)_7$ ) and 0.83 (3H, t,  $J$  7,  $\text{CH}_3$ ).

$^{13}\text{C}$  NMR ( $\delta_{\text{C}}$ , 125 MHz,  $\text{CDCl}_3$ ): 175.8, 155.9 (CO), 65.0 ( $\text{OCH}_2$ ), 53.5 (NHCHCO), 42.0 (NCH<sub>2</sub>), 32.1, 31.8, 29.5 ( $\times 2$ ), 29.2 ( $\times 2$ ), 29.0, 28.8, 28.0, 25.8, 22.6 ( $\text{CH}_2$ ) and 14.1 ( $\text{CH}_3$ ).  
m/z ( $\text{C}_{17}\text{H}_{32}\text{N}_2\text{O}_3\text{Na}$ ): 335.23190 (calculated: 335.2311).

**Example 14: (S)-(E)-3-(dodec-2-enoyl)amino-caprolactam:**

10 (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (2 mmol) and  $\text{Na}_2\text{CO}_3$  (6 mmol) in water (25 ml) were added to a solution of dodec-2-enoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane ( $2 \times 25$  ml). The combined organic 15 layers were dried over  $\text{Na}_2\text{CO}_3$  and reduced *in vacuo*. The residue was purified by silica column chromatography (eluent: EtOAc to 9:1 EtOAc:MeOH) to give the title compound (472 mg; 77%).

Melting point: 87-88 °C.

$[\alpha]_D^{25}$  ( $c = 1$ ,  $\text{CHCl}_3$ ) = +44.7.

20 IR:  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3382, 3331 (NH), 1660, 1616 (CO), 1520 (NH).  
 $^1\text{H}$  NMR ( $\delta_{\text{H}}$ , 500 MHz,  $\text{CDCl}_3$ ): 6.94 (1H, d,  $J$  5.5,  $\text{CHNH}$ ), 6.84 (1H, br s,  $\text{CH}_2\text{NH}$ ), 6.78 (1H, dt,  $J$  15.5, 7,  $\text{CH}_2\text{CH}=\text{CH}$ ), 5.80 (1H, d,  $J$  15.5,  $\text{CH}_2\text{CH}=\text{CH}$ ), 4.56 (1H, ddd,  $J$  11, 6, 1.5,  $\text{CHNH}$ ), 3.29-3.15 (2H, m,  $\text{CH}_2\text{NH}$ ), 2.11 (2H, q,  $J$  7,  $\text{CH}_2\text{CH}=\text{CH}$ ),  
25 2.07 (1H, br d,  $J$  13.5, ring CH), 1.98-1.90 (1H, m, ring CH), 1.86-1.73 (2H, m, ring CH), 1.44 (1H, br qd,  $J$  14, 2.5, ring CH), 1.41-1.29 (3H, br m, ring CH +  $\text{CH}_2\text{CH}_2\text{CH}=\text{CH}$ ), 1.29-1.14 (12H, m,  $(\text{CH}_2)_6$ ) and 0.82 (3H, t,  $J$  6.5,  $\text{CH}_3$ ).  
 $^{13}\text{C}$  NMR ( $\delta_{\text{C}}$ , 125 MHz,  $\text{CDCl}_3$ ): 175.9, 165.0 (CO), 144.8, 123.5 ( $\text{CH}=\text{CH}$ ), 52.0 (NHCHCO), 42.0 (NCH<sub>2</sub>), 32.0, 31.8, 31.6, 29.4 ( $\times 2$ ), 29.2, 29.1, 28.8, 28.2, 27.9, 22.6 ( $\text{CH}_2$ ) and 14.1 ( $\text{CH}_3$ ).  
30 m/z ( $\text{C}_{18}\text{H}_{32}\text{N}_2\text{O}_2\text{Na}$ ): 331.23570 (calculated: 331.2361).

**Example 15: (S)-3-(dec-9-enylaminocarbonyl)amino-caprolactam:**

(*S,S*)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (2 mmol) and Na<sub>2</sub>CO<sub>3</sub> (6 mmol) in water (25 ml) were added to a solution of dec-9-enyl isocyanate (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na<sub>2</sub>CO<sub>3</sub> and reduced *in vacuo*. The residue was purified by silica column chromatography (eluent: EtOAc to 9:1 EtOAc:MeOH) to give the title compound (347 mg; 56%).

Melting point: 98-99 °C.

10 [α]<sub>D</sub><sup>25</sup> (c = 1, CHCl<sub>3</sub>) = +27.3.

IR: ν<sub>max</sub> (cm<sup>-1</sup>): 3365, 3327, 3276 (NH), 1619, (CO), 1551 (NH).

<sup>1</sup>H NMR (δ<sub>H</sub>, 500 MHz, CDCl<sub>3</sub>): 6.64 (1H, br s, ring CH<sub>2</sub>NH), 6.12 (1H, d, *J* 6 CHNH), 5.75 (1H, ddtd, *J* 17, 10, 6.5, 1.5, CH<sub>2</sub>=CH), 5.21-5.12 (1H, br m, urea CH<sub>2</sub>NH),

15 4.93 (1H, dq, *J* 17, 1.5, CHH=CH), 4.87 (1H, br d, *J* 10, CHH=CH), 4.49 (1H, dd, *J* 11, 6, NHCHCO), 3.25 (1H, ddd, *J* 15.5, 12, 4, ring CH<sub>2</sub>N), 3.17 (1H, dt, *J* 14, 6, ring CH<sub>2</sub>N), 3.11-3.02 (2H, m, urea NHCH<sub>2</sub>), 2.05-1.87 (4H, br m, ring CH ×2 + CH<sub>2</sub>CH=CH), 1.82-1.70 (2H, m, ring CH), 1.48-1.36 (3H, br m, chain CH<sub>2</sub>CH<sub>2</sub>NH, + ring CH), 1.36-1.27 (3H, m, ring CH + chain CH<sub>2</sub>) and 1.27-1.17 (8H, m, chain (CH<sub>2</sub>)<sub>4</sub>).

<sup>13</sup>C NMR (δ<sub>C</sub>, 125 MHz, CDCl<sub>3</sub>): 177.2, 157.6 (CO), 139.1, 114.1 (CH=CH), 52.7 (NHCHCO), 42.1, 40.3 (NCH<sub>2</sub>), 33.7, 32.9, 30.3, 29.4, 29.3, 29.0, 28.8 (×2), 27.9 and 26.9 (CH<sub>2</sub>).

m/z (C<sub>17</sub>H<sub>31</sub>N<sub>3</sub>O<sub>2</sub>Na): 332.23150 (calculated: 332.2314).

25

**Example 16:** (*S*)-3-(decylaminocarbonyl)amino-caprolactam:

(*S,S*)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (2 mmol) and Na<sub>2</sub>CO<sub>3</sub> (6 mmol) in water (25 ml) were added to a solution of decyl isocyanate (2 mmol) in

30 dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na<sub>2</sub>CO<sub>3</sub> and reduced *in vacuo*. The residue was purified by

silica column chromatography (eluent: EtOAc to 9:1 EtOAc:MeOH) to give the title compound (401 mg, 64%).

Melting point: 97-98 °C.

$[\alpha]_D^{25}$  ( $c = 1$ , CHCl<sub>3</sub>) = +27.7.

- 5 IR:  $\nu_{\text{max}}$  (cm<sup>-1</sup>): 3359, 3316 (NH), 1621, (CO), 1558 (NH).  
<sup>1</sup>H NMR ( $\delta_H$ , 500 MHz, CDCl<sub>3</sub>): 6.62 (1H, br s, ring CH<sub>2</sub>NH), 6.09 (1H, d,  $J$  6 CHNH), 5.16 (1H, br t,  $J$  5, urea CH<sub>2</sub>NH), 4.48 (1H, ddd,  $J$  11, 6, 1, NHCHCO), 3.26 (1H, ddd,  $J$  16, 11, 5, ring CH<sub>2</sub>N), 3.17 (1H, dt,  $J$  15, 7, ring CH<sub>2</sub>N), 3.11-3.02 (2H, m, urea NHCH<sub>2</sub>), 2.02 (1H, br d  $J$  14, ring CH), 1.96-1.87 (1H, m, ring CH), 10 1.83-1.70 (2H, m, ring CH), 1.48-1.27 (4H, br m, ring CH  $\times$  2 + chain CH<sub>2</sub>), 1.27-1.14 (14H, m, (CH<sub>2</sub>)<sub>7</sub>) and 0.82 (3H, t,  $J$  7, CH<sub>3</sub>).  
<sup>13</sup>C NMR ( $\delta_C$ , 125 MHz, CDCl<sub>3</sub>): 177.2, 157.6 (CO), 52.7 (NHCHCO), 42.1, 40.4 (NCH<sub>2</sub>), 32.9, 31.8, 30.2, 29.6, 29.5, 29.4, 29.3, 28.8, 27.9, 26.9, 22.6 (CH<sub>2</sub>) and 14.1.  
15 m/z (C<sub>17</sub>H<sub>33</sub>N<sub>3</sub>O<sub>2</sub>Na): 334.24880 (calculated: 334.2470).

**Example 17: (R)-3-(2',2'-Dimethyl-dodecanoyl)amino-caprolactam:**

- (R,R)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate **2** (2 mmol) and Na<sub>2</sub>CO<sub>3</sub> (6 mmol) in water (25 ml) were added to a solution of 2,2-dimethyl-dodecanoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction was stirred for 2 hours. The organic layer was then separated and 20 the aqueous phase was extracted with additional dichloromethane (2  $\times$  25 ml). The combined organic layers were dried over Na<sub>2</sub>CO<sub>3</sub> and reduced *in vacuo*. The residue was purified by silica column chromatography (EtOAc: hexanes 1:3 to EtOAc) to give (R)-3-(2',2'-dimethyl-dodecanoyl)amino-caprolactam (515 mg, 76%); m.p. 48-49 °C;  $[\alpha]_D^{25}$  ( $c = 1$ , CHCl<sub>3</sub>) -25.7;  $[\alpha]_D^{25}$  ( $c = 0.5$ , MeOH) -12.2.

25

**Example 18 : (S)-3-(2',2'-Dimethyl-pentanoyl)amino-caprolactam:**

- (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate **2** (20 mmol) and Na<sub>2</sub>CO<sub>3</sub> (60 mmol) in water (50 ml) were added to a solution of 2,2-dimethyl-pentanoyl chloride (20 mmol) in dichloromethane (50 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and 30 the aqueous phase was extracted with additional dichloromethane (2  $\times$  25 ml). The combined organic layers were dried over Na<sub>2</sub>CO<sub>3</sub> and reduced *in vacuo*. The residue

was recrystallised from EtOAc / hexane to give (*S*)-3-(2',2'-dimethyl-pentanoyl)amino-caprolactam (3.50 g, 77%); m.p. 84-85 °C;  $[\alpha]_D^{25}$  (c = 1, CHCl<sub>3</sub>) +30.7;  $\nu_{\text{max}}/\text{cm}^{-1}$  3387, 3239 (NH), 1655, 1634 (CO), 1507 (NH); δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 7.08 (1H, d, J 5, CHNH), 6.53 (1H, br s, CH<sub>2</sub>NH), 4.45 (1H, ddd, J 11, 5.5, 1.5, CHNH), 3.29-3.16 (2H, m, CH<sub>2</sub>NH), 2.00 (1H, br d, J 13, ring CH), 1.98-1.92 (1H, m, ring CH), 1.84-1.73 (2H, m, ring CH), 1.47-1.30 (4H, br m, ring CH × 2 + CH<sub>2</sub>CMe<sub>2</sub>CONH), 1.23-1.15 (2H, m, CH<sub>2</sub>CH<sub>3</sub>) 1.14 (3H, s, CMeMe), 1.13 (3H, s, CMeMe) and 0.84 (3H, t, J 7, CH<sub>2</sub>CH<sub>3</sub>); δ<sub>C</sub> (125 MHz, CDCl<sub>3</sub>) 177.0, 176.1 (CO), 52.1 (NHCHCO), 43.6, 42.0 (×2, one of which is CMe<sub>2</sub>), 31.5, 28.9, 27.9 (CH<sub>2</sub>), 25.3, 25.2 (CH<sub>3</sub>), 18.0 (CH<sub>2</sub>) and 14.5 (CH<sub>3</sub>); m/z (M<sup>+</sup> C<sub>13</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub> requires 240.18378) 240.18437.

**Example 19 :** (*S*)-3-(2',2'-Dimethyl-pent-4-enoyl)amino-caprolactam:  
*(S,S)*-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate **2** (20 mmol) and  
15 Na<sub>2</sub>CO<sub>3</sub> (60 mmol) in water (50 ml) were added to a solution of 2,2-dimethyl-pent-4-enoyl chloride (20 mmol) in dichloromethane (50 ml) at ambient temperature and the reaction was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na<sub>2</sub>CO<sub>3</sub> and reduced *in vacuo*. The residue  
20 was purified by silica column chromatography (1:1 EtOAc: hexane to EtOAc) to give (*S*)-3-(2',2'-dimethyl-pent-4-enoyl)amino-caprolactam (1.43 g, 32%); m.p. 71-72 °C;  $[\alpha]_D^{25}$  (c = 1, CHCl<sub>3</sub>) +27.7;  $\nu_{\text{max}}/\text{cm}^{-1}$  3395, 3304 (NH), 1675, 1633 (CO), 1534 (NH); δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 7.10 (1H, d, J 4.5, CHNH), 6.48 (1H, br s, CH<sub>2</sub>NH), 5.68 (1H, ddt, J 17, 10, 7.5, CH=CH<sub>2</sub>), 5.02 (1H, br d, J 17 CH=CHH),  
25 5.00 (1H, br d, J 10, CH=CHH), 4.45 (1H, dd, J 11, 5.5, CHNH), 3.30-3.17 (2H, m, CH<sub>2</sub>NH), 2.27 (1H, J 14, 7.5, CHHCH=CH<sub>2</sub>), 2.22 (1H, dd, J 14, 7.5, CHHCH=CH<sub>2</sub>), 2.01 (1H, br d, J 13, ring CH), 1.98-1.92 (1H, m, ring CH), 1.85-1.73 (2H, m, ring CH), 1.47-1.30 (2H, br m, ring CH × 2), 1.16 (3H, s, CMeMe) and 1.15 (3H, s, CMeMe); δ<sub>C</sub> (125 MHz, CDCl<sub>3</sub>) 176.4, 175.9 (CO), 134.2 (CH=CH<sub>2</sub>),  
30 117.8 (CH=CH<sub>2</sub>), 52.1 (NHCHCO), 45.2, 42.1 (CH<sub>2</sub>), 41.9 (CMe<sub>2</sub>), 31.5, 28.9, 27.9 (CH<sub>2</sub>), 25.0 and 24.9 (CH<sub>3</sub>); m/z (M<sup>+</sup> C<sub>13</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub> requires 238.16813) 238.16834.

**Example 20:** (*S*)-3-(2',2'-Dimethyl-propionyl)amino-caprolactam: (*S,S*)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate **2** (5 mmol) and Na<sub>2</sub>CO<sub>3</sub> (15 mmol) in water (15 ml) were added to a solution of 2,2-dimethyl-propionyl chloride (5 mmol) in dichloromethane (15 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and reduced *in vacuo*. The residue was recrystallised from EtOAc / hexane to give (*S*)-3-(2',2'-dimethyl-propionyl)amino-caprolactam (645 mg, 61%); m.p. 126-127 °C; [α]<sub>D</sub><sup>25</sup> (c = 1, CHCl<sub>3</sub>) +39.5; ν<sub>max</sub>/cm<sup>-1</sup> 10 3381, 3255 (NH), 1680, 1632 (CO), 1506 (NH); δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 7.10 (1H, d, *J* 5.0, CHNH), 6.75 (1H, br s, CH<sub>2</sub>NH), 4.42 (1H, ddd, *J* 11, 5.5, 1.5, CHNH), 3.27-3.16 (2H, m, CH<sub>2</sub>NH), 2.03-1.89 (2H, m, 2 × ring CH), 1.83-1.71 (2H, m, 2 × ring CH), 1.45-1.28 (2H, m, 2 × ring CH) and 1.15 (9H, s, 3 × CH<sub>3</sub>); δ<sub>C</sub> (125 MHz, CDCl<sub>3</sub>) 177.7, 176.1 (CO), 52.1 (NHCHCO), 42.0 (CH<sub>2</sub>N), 40.5 (CCO), 31.5, 28.9, 15 27.9 (CH<sub>2</sub> lactam), 27.4 (3 × CH<sub>3</sub>);

**Example 21:** (*S*)-3-(2',2'-Dimethyl-butyryl)amino-caprolactam:

(*S,S*)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate **2** (5 mmol) and Na<sub>2</sub>CO<sub>3</sub> (15 mmol) in water (15 ml) were added to a solution of 2,2-dimethyl-butyryl chloride (5 mmol) in dichloromethane (15 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and reduced *in vacuo*. The residue was recrystallised from EtOAc / hexane to give (*S*)-3-(2',2'-dimethyl-propionyl)amino-caprolactam (562 mg, 50%); m.p. 106-107 °C; [α]<sub>D</sub><sup>25</sup> (c = 1, CHCl<sub>3</sub>) +33.6; ν<sub>max</sub>/cm<sup>-1</sup> 3400, 3278 (NH), 1677, 1630 (CO), 1500 (NH); δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 7.08 (1H, d, *J* 5.0, CHNH), 6.72 (1H, br s, CH<sub>2</sub>NH), 4.44 (1H, ddd, *J* 11, 5.5, 1.5, CHNH), 3.28-3.16 (2H, m, CH<sub>2</sub>NH), 2.04-1.90 (2H, m, 2 × ring CH), 1.83-1.72 (2H, m, 2 × ring CH), 1.57-1.44 (2H, m, CH<sub>2</sub>CH<sub>3</sub>), 1.44-1.30 (2H, m, 2 × ring CH) 1.12 (3H, s, CH<sub>3</sub>) 1.11 (3H, s, CH<sub>3</sub>) and 0.78 (3H, t, *J* 7.5, CH<sub>2</sub>CH<sub>3</sub>); δ<sub>C</sub> (125 MHz, CDCl<sub>3</sub>) 177.0, 176.0 (CO), 52.1 (NHCHCO), 42.2 (CCO), 42.0 (CH<sub>2</sub>N), 30 33.7 (CH<sub>2</sub>CH<sub>3</sub>), 31.6, 28.9, 27.9 (CH<sub>2</sub> lactam), 24.8, 24.7 (CCH<sub>3</sub>) and 9.1 (CH<sub>2</sub>CH<sub>3</sub>); m/z (MH<sup>+</sup> C<sub>12</sub>H<sub>23</sub>N<sub>2</sub>O<sub>2</sub> requires 227.1760) 227.1767.

**Example 22:** (*S,E*)-3-(2',2'-Dimethyl-dodec-4'-enoyl)amino-caprolactam:

(*S,S*)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate **2** (10 mmol) and Na<sub>2</sub>CO<sub>3</sub> (30 mmol) in water (30 ml) were added to a solution of 2,2-dimethyl-dodec-2-enoyl chloride (crude, from above reaction) (10 mmol) in dichloromethane

- 5 (30 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na<sub>2</sub>CO<sub>3</sub> and reduced *in vacuo*. The residue was purified by silica column chromatography (1:1 EtOAc: hexanes to EtOAc) to give (*S,E*)-3-(2',2'-dimethyl-dodec-4'-enoyl)amino-caprolactam as a colourless oil (2.12 g, 63%); [α]<sub>D</sub><sup>25</sup> (c = 1, CHCl<sub>3</sub>) +21.6; ν<sub>max</sub>/cm<sup>-1</sup> 3264 (NH), 1639 (CO), 1497 (NH); δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 7.09 (1H, d, *J* 5.5, CHNH), 6.67-6.32 (1H, br m, CH<sub>2</sub>NH), 5.42 (1H, dt, *J* 15, 6.5, CH=CH), 5.28 (1H, dt, *J* 15, 7, CH=CH), 4.44 (1H, dd, *J* 11, 5.5, CHNH), 3.30-3.17 (2H, m, CH<sub>2</sub>NH), 2.20 (1H, dd, 13.5, 7, CH=CHCH<sub>2</sub>), 2.14 (1H, dd, 13.5, 7, CH=CHCH<sub>2</sub>), 2.01-1.87 (4H, br m, ring CH × 2, + CH<sub>2</sub>CH=CH), 1.87-1.74 (2H, m, ring CH), 1.47-1.32 (2H, m, ring CH), 1.27-1.15 (10H, br m, (CH<sub>2</sub>)<sub>5</sub>) 1.13 (3H, s, CMeMe), 1.12 (3H, s, CMeMe) and 0.83 (3H, t, *J* 7, CH<sub>2</sub>CH<sub>3</sub>); δ<sub>C</sub> (125 MHz, CDCl<sub>3</sub>) 176.8, 176.0 (CO), 134.2, 125.2 (CH=CH), 52.1 (NHCHCO), 43.9 (CH<sub>2</sub>), 42.1 (×2) (CH<sub>2</sub> + CMe<sub>2</sub>), 32.6, 31.8, 31.5, 30.1, 29.4, 29.1 (×2), 28.9, 27.9 (CH<sub>2</sub>),
- 10 25.0, 24.8 (CH<sub>3</sub>) and 22.6 (CH<sub>3</sub>); m/z (MH<sup>+</sup> C<sub>20</sub>H<sub>37</sub>N<sub>2</sub>O<sub>2</sub> requires 337.2855) 337.2858.
- 15
- 20

**Example 23:** (*S*)-3-(2',2',5'-Trimethyl-hex-4'-enoyl)amino-caprolactam:

(*S,S*)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate **2** (4.11 g, 16 mmol)

- 25 and Na<sub>2</sub>CO<sub>3</sub> (5.09 g, 48 mmol) in water (50 ml) were added to a solution of 2,2,5-trimethyl-hex-4-enoyl chloride (16 mmol) in dichloromethane (50 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 50 ml). The combined organic layers were dried over Na<sub>2</sub>CO<sub>3</sub> and reduced *in vacuo*. The residue was purified by silica column chromatography (1:5 EtOAc: hexanes to EtOAc) to give (*S*)-3-(2',2',5'-trimethyl-hex-4'-enoyl)amino-caprolactam as a waxy solid (3.58 g, 84%); m.p. 43-44 °C; [α]<sub>D</sub><sup>25</sup> (c = 1, CHCl<sub>3</sub>) +23.2; ν<sub>max</sub>/cm<sup>-1</sup> 3394, 3251 (NH), 1674, 1633 (CO), 1503 (NH); δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 7.11 (1H, d, *J* 5.0, CHNH), 6.65-6.45 (1H, br m, CH<sub>2</sub>NH), 5.04 (1H, t, *J*
- 30

7.5, CH=C), 4.44 (1H, ddd, *J* 11, 5.5, 1.5, CHNH), 3.24-3.16 (2H, m, CH<sub>2</sub>NH), 2.20 (1H, dd, *J* 14.5, 7.5, C=CHCH<sub>2</sub>), 2.15 (1H, dd, *J*, 14.5, 7.5, C=CHCH<sub>2</sub>), 2.03-1.90 (2H, m, 2 × ring CH), 1.84-1.72 (2H, m, 2 × ring CH), 1.65 (3H, s, CH<sub>3</sub>), 1.56 (3H, s, CH<sub>3</sub>), 1.45-1.28 (2H, m, 2 × ring CH), 1.13 (3H, s, CH<sub>3</sub>) and 1.12 (3H, s, CH<sub>3</sub>); δ<sub>C</sub> (125 MHz, CDCl<sub>3</sub>) 176.9, 176.0 (CO), 134.1, 119.9 (CH=CH), 52.1 (NHCHCO), 42.5 (CH<sub>2</sub>CMe<sub>2</sub>), 42.1 (CH<sub>2</sub>N), 39.0, 31.5, 28.9, 28.0 (CH<sub>2</sub> lactam), 26.0, 25.0, 24.9, 17.9 (CH<sub>3</sub>); m/z (MH<sup>+</sup> C<sub>15</sub>H<sub>27</sub>N<sub>2</sub>O<sub>2</sub> requires 267.2073) 267.2063.

**Example 24:** (*S*)-3-(2',2',5'-Trimethyl-hexanoyl)amino-caprolactam:

(S)-3-(2',2',5'-trimethyl-hex-4'-enoyl)amino-caprolactam (400 mg) was dissolved in EtOAc (25 ml), palladium hydroxide-on-carbon (20%, *ca* 100 mg) was added, and the mixture was stirred at ambient temperature under an atmosphere of hydrogen for 14 hours. The reaction was then filtered through a Celite® pad and the solvent was removed *in vacuo* to give (*S*)-3-(2',2',5'-yrimethyl-hexanoyl)amino-caprolactam as a waxy solid (400 mg, 98%); m.p. 73-74 °C; [α]<sub>D</sub><sup>25</sup> (c = 1, CHCl<sub>3</sub>) +27.8; ν<sub>max</sub>/cm<sup>-1</sup> 3249 (NH), 1654, 1638 (CO), 1502 (NH); δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 7.08 (1H, d, *J* 5.0, CHNH), 6.75-6.55 (1H, br m, CH<sub>2</sub>NH), 4.44 (1H, ddd, *J* 11, 5.5, 1.5, CHNH), 3.29-3.16 (2H, m, CH<sub>2</sub>NH), 2.03-1.91 (2H, m, 2 × ring CH), 1.84-1.73 (2H, m, 2 × ring CH), 1.47-1.28 (5H, m, 2 × ring CH + CH<sub>2</sub> + CH(CH<sub>3</sub>)<sub>2</sub>), 1.13 (3H, s, CH<sub>3</sub>), 1.12 (3H, s, CH<sub>3</sub>), 1.08-1.02 (2H, m, CH<sub>2</sub>), 0.82 (3H, s, CH<sub>3</sub>), 0.80 (3H, s, CH<sub>3</sub>); δ<sub>C</sub> (125 MHz, CDCl<sub>3</sub>) 177.1, 176.1 (CO), 52.1 (NHCHCO), 42.1 (CH<sub>2</sub>N), 41.9 (CH<sub>2</sub>CMe<sub>2</sub>), 39.0, 33.7, 31.5, 28.9 (CH<sub>2</sub>), 28.4 (Me<sub>2</sub>CH), 27.9 (CH<sub>2</sub>), 25.3, 25.2, 22.6, 22.5 (CH<sub>3</sub>); m/z (MH<sup>+</sup> C<sub>15</sub>H<sub>29</sub>N<sub>2</sub>O<sub>2</sub> requires 269.2229) 269.2219.

NEED MS(sub) EA

**Example 25:** (*S*)-3-(11'-bromo-undecanoyl)amino-caprolactam:

(S)-3-amino-caprolactam hydrochloride 1 (5 mmol) and Na<sub>2</sub>CO<sub>3</sub> (15 mmol) in water (25 ml) were added to a solution of 11-bromo-undecanoyl chloride (5 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction was stirred for 4 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na<sub>2</sub>CO<sub>3</sub> and reduced *in vacuo*. The residue was purified by recrystallisation from EtOAc to give (*S*)-3-(11'-bromo-undecanoyl)amino-caprolactam (1.49 g, 79%); m.p. (EtOAc) 73-74 °C; [α]<sub>D</sub><sup>25</sup> (c = 1, CHCl<sub>3</sub>) +31.8;

$\nu_{\text{max}}$ /cm<sup>-1</sup> 3342, 3287 (NH), 1668, 1634 (CO), 1515 (NH);  $\delta_{\text{H}}$  (500 MHz, d<sub>6</sub>-DMSO) 7.76 (1H, t, J 6.5, CH<sub>2</sub>NH), 7.67 (1H, d, J 7, CHNH), 4.38 (1H, dd, J 11, 7, CHNH), 3.51 (2H, t, J 6.5, CH<sub>2</sub>Br), 3.15 (1H, ddd, J 15.5, 10.5, 5, CHHNH), 3.05 (1H, dt, J 14, 7, CHHNH), 2.17-2.06 (2H, m, CH<sub>2</sub>CONH), 1.85 (1H, dt, J 14, 3, C-5 H), 1.82-1.68 (4H, m, C-4 H, C-6 H and CH<sub>2</sub>CH<sub>2</sub>Br), 1.62 (1H, qt, J 12, 3.5, C-5 H), 1.46 (2H, br qn J 6.5, CH<sub>2</sub>CH<sub>2</sub>CONH), 1.41-1.31 (3H, m, C-4 H and chain CH<sub>2</sub>) and 1.31-1.13 (11H, m, (CH<sub>2</sub>)<sub>5</sub> + C-6 H);  $\delta_{\text{C}}$  (125 MHz, d<sub>6</sub>-DMSO) 174.4 (CO-ring), 171.3 (CO-chain), 51.3 (NHCHCO), 40.7 (NCH<sub>2</sub>), 35.3, 35.2, 32.4, 31.3, 29.0, 28.9 ( $\times$ 3), 28.7, 28.2, 27.8, 27.6 and 25.4 (CH<sub>2</sub>); m/z (MH<sup>+</sup> BrC<sub>17</sub>H<sub>32</sub>N<sub>2</sub>O<sub>2</sub> requires 375.1647) 375.1655.

**Example 26 : (S)-3-(11'-azido-undecanoyl)amino-caprolactam:**

Sodium azide (650 mg, 10 mmol) was added to (S)-3-(11'-bromo-undecanoyl)amino-caprolactam (375 mg, 1 mmol) in DMF (2 ml) and the mixture  
5 was heated at 60 °C for 14 hours. The solvent was then removed *in vacuo* and the residue was partitioned between water (20 ml) and EtOAc (3  $\times$  20 ml). The combined organic layers were washed with 1M HCl<sub>aq</sub> (2  $\times$  20 ml) and then dried over Na<sub>2</sub>CO<sub>3</sub> and reduced *in vacuo*. The residue was purified by recrystallisation from EtOAc to give (S)-3-(11'-azido-undecanoyl)amino-caprolactam (221 mg,  
10 66%); m.p. (EtOAc) 71-72 °C;  $[\alpha]_D^{25}$  (c = 1, CHCl<sub>3</sub>) +34.7;  $\nu_{\text{max}}$ /cm<sup>-1</sup> 3344, 3289 (NH), 2101 (N<sub>3</sub>) 1668, 1631 (CO), 1516 (NH);  $\delta_{\text{H}}$  (500 MHz, d<sub>6</sub>-DMSO) 7.77 (1H, t, J 6, CH<sub>2</sub>NH), 7.67 (1H, d, J 7, CHNH), 4.38 (1H, dd, J 11, 7, CHNH), 3.30 (2H, t, J 7, CH<sub>2</sub>N<sub>3</sub>), 3.15 (1H, ddd, J 15.5, 10.5, 5, CHHNH), 3.05 (1H, dt, J 14, 5.5, CHHNH), 2.17-2.07 (2H, m, CH<sub>2</sub>CONH), 1.85 (1H, dt, J 14, 3.5, C-5 H), 1.82-1.68 (2H, m, C-4 H, C-6 H), 1.62 (1H, qt, J 13, 3.5, C-5 H), 1.51 (4H, m, CH<sub>2</sub>CH<sub>2</sub>CONH and CH<sub>2</sub>CH<sub>2</sub>N<sub>3</sub>), 1.36 (1H, qd, J 13, 3, C-4 H), and 1.33-1.13 (13H, m, (CH<sub>2</sub>)<sub>6</sub> + C-6 H);  $\delta_{\text{C}}$  (125 MHz, d<sub>6</sub>-DMSO) 174.4 (CO-ring), 171.3 (CO-chain), 51.3 (NHCHCO), 50.7 (CH<sub>2</sub>N<sub>3</sub>), 40.7 (NCH<sub>2</sub>), 35.3, 31.3, 29.0 ( $\times$ 2), 28.9, 28.7, 28.6, 28.3, 27.8, 26.2 and 25.4 (CH<sub>2</sub>); m/z (MNa<sup>+</sup> C<sub>17</sub>H<sub>31</sub>N<sub>5</sub>O<sub>2</sub>Na requires 360.2375)  
15 360.2360.

**Example 27: (S) Sodium 3-(undecanoyl)amino-caprolactam 11'-sulfonate tetrahydrate:**

sodium sulfite (630 mg, 5 mmol) in water (3 ml) was added to (S)-3-(11-bromo-undecanoyl)amino-caprolactam (375 mg, 1 mmol) in ethanol (2 ml) and the mixture  
5 was heated at reflux for 14 hours. The cooled reaction mixture was then added to ethanol (25 ml) and the reaction was filtered. The solvent was then removed *in vacuo* to give (S) sodium 3-(undecanoyl)amino-caprolactam 11'-sulfonate tetrahydrate (456 mg, 97%); m.p. (EtOAc) 208-210 °C;  $[\alpha]_D^{25}$  ( $c = 1, H_2O$ ) -15.5;  
10  $\nu_{max}/cm^{-1}$  3430, 3344, 3289 (NH + H<sub>2</sub>O), 1667, 1643 (CO), 1530 (NH) 1195, 1183 (SO<sub>3</sub>, asymm.), 1064 (SO<sub>3</sub>, symm.);  $\delta_H$  (500 MHz, d<sub>6</sub>-DMSO) 7.76 (1H, t, J 6, CH<sub>2</sub>NH), 7.70 (1H, d, J 7, CHNH), 4.35 (1H, dd, J 10, 7.5, CHNH), 3.42 (8H, s, 4 × H<sub>2</sub>O) 3.17-3.00 (2H, m, CH<sub>2</sub>NH), 2.47-2.38 (2H, m, CH<sub>2</sub>SO<sub>3</sub>), 2.17-2.05 (2H, m, CH<sub>2</sub>CONH), 1.82 (1H, br s, J 13.5, C-5 H), 1.75-1.66 (2H, m, C-4 H, C-6 H), 1.65-1.50 (3H, m, C-5 H + chain CH<sub>2</sub>), 1.47-1.40 (2H, m, chain CH<sub>2</sub>) 1.35 (1H, qd, J 13, 3, C-4 H), and 1.30-1.11 (13H, m, (CH<sub>2</sub>)<sub>6</sub> + C-6 H);  $\delta_C$  (125 MHz, d<sub>6</sub>-DMSO) 174.5 (CO-ring), 171.5 (CO-chain), 51.6 (CH<sub>2</sub>SO<sub>3</sub>), 51.4 (NHCHCO), 40.8 (NCH<sub>2</sub>), 35.3, 31.3, 29.1 (×3), 29.0 (×2), 28.8, 28.6, 27.8, 25.5 and 25.1 (CH<sub>2</sub>); m/z (MNa<sup>+</sup> C<sub>17</sub>H<sub>31</sub>N<sub>2</sub>O<sub>5</sub>SNa<sub>2</sub> requires 421.1749) 421.1748.

20 **Example 28: (S)-3-(Decanesulfonyl)amino-caprolactam:**

(S)-3-amino-caprolactam hydrochloride 1 (3 mmol) and Na<sub>2</sub>CO<sub>3</sub> (9 mmol) in water (20 ml) were added to a solution of decanesulfonylchloride (3 mmol) in dichloromethane (20 ml) at ambient temperature and the reaction was stirred for 10 hours. The organic layer was then separated and the aqueous phase was extracted  
25 with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na<sub>2</sub>CO<sub>3</sub> and reduced *in vacuo*. The residue was purified by recrystallisation from EtOAc / hexanes to give (S)-3-(decanesulfonyl)amino-caprolactam (481 mg, 48%); m.p. 98-99 °C;  $[\alpha]_D^{25}$  ( $c = 1, MeOH$ ) +22.7;  $\nu_{max}/cm^{-1}$  3365, 3248 (NH), 1657 (CO), 1324, 1142 (SO<sub>2</sub>N);  $\delta_H$  (500 MHz, CDCl<sub>3</sub>) 6.35-6.18 (1H, m, CH<sub>2</sub>NH), 5.71 (1H, d, J 6, CHNH), 4.11 (1H, ddd, J 11.5, 6, 2, CHNH), 3.31-3.18 (2H, m, CH<sub>2</sub>NH), 2.98-2.92 (2H, m, CH<sub>2</sub>SO<sub>2</sub>), 2.09 (1H, br d, J 14, ring CH), 2.06-1.97 (1H, m, ring CH), 1.88-1.59 (5H, m, CH<sub>2</sub>CH<sub>2</sub>SO<sub>2</sub> + 3 ring CH), 1.43-1.33 (3H, m, chain CH<sub>2</sub> + ring CH), 1.32-1.18 (12H, m, CH<sub>3</sub>(CH<sub>2</sub>)<sub>6</sub>) and 0.86 (3H, m, CH<sub>3</sub>);  $\delta_C$  (125 MHz, CDCl<sub>3</sub>) 174.8 (CO) 55.5 (NHCHCO), 53.5 (CH<sub>2</sub>SO<sub>2</sub>),

40.7 (NCH<sub>2</sub>), 33.9, 31.8, 29.4, 29.3, 29.2, 29.1, 28.6, 28.3, 27.9, 23.5, 22.6 (CH<sub>2</sub>), and 14.1 (CH<sub>3</sub>); m/z (MNa<sup>+</sup> C<sub>16</sub>H<sub>32</sub>N<sub>2</sub>O<sub>3</sub>SNa requires 355.2031) 355.2054; anal (C<sub>16</sub>H<sub>32</sub>N<sub>2</sub>O<sub>3</sub>S requires C, 57.8, H, 9.7, N, 8.4) C, 57.8, H, 9.7, N, 8.3.

5   **Example 29: (S)-3-(Dodecanesulfonyl)amino-caprolactam:**

(S)-3-amino-caprolactam hydrochloride **1** (2 mmol) and Na<sub>2</sub>CO<sub>3</sub> (6 mmol) in water (20 ml) were added to a solution of dodecanesulfonylchloride (2 mmol) in dichloromethane (20 ml) at ambient temperature and the reaction was stirred for 10 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na<sub>2</sub>CO<sub>3</sub> and reduced *in vacuo*. The residue was purified by silica column chromatography (hexanes:EtOAc 3:1 to 100% EtOAc) and then by recrystallisation from heptane to give (S)-3-(dodecanesulfonyl)amino-caprolactam (302 mg, 42%); m.p. 100-101 °C; [α]<sub>D</sub><sup>25</sup> (c = 1, MeOH) +22.4; ν<sub>max</sub>/cm<sup>-1</sup> 3366, 3247 (NH),

15   1657 (CO), 1324, 1143 (SO<sub>2</sub>N); δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 6.66 (1H, t, *J* 6, CH<sub>2</sub>NH), 5.78 (1H, d, *J* 6, CHNH), 4.10 (1H, ddd, *J* 11, 6, 2, CHNH), 3.29-3.17 (2H, m, CH<sub>2</sub>NH), 2.97-2.90 (2H, m, CH<sub>2</sub>SO<sub>2</sub>), 2.12-2.03 (1H, m, ring CH), 2.03-1.96 (1H, m, ring CH), 1.88-1.59 (5H, m, CH<sub>2</sub>CH<sub>2</sub>SO<sub>2</sub> + 3 ring CH), 1.43-1.32 (3H, m, ring CH + chain CH<sub>2</sub>), 1.32-1.18 (16H, m) and 0.85 (3H, m, CH<sub>3</sub>); δ<sub>C</sub> (125 MHz, CDCl<sub>3</sub>)

20   175.0 (CO) 55.5 (NHCHCO), 53.5 (CH<sub>2</sub>SO<sub>2</sub>), 42.1 (NCH<sub>2</sub>), 33.8, 31.8, 29.6 (×2), 29.5, 29.3 (×2), 29.1, 28.6, 28.3, 27.9, 23.5, 22.6 (CH<sub>2</sub>), and 14.1 (CH<sub>3</sub>); m/z (MNa<sup>+</sup> C<sub>18</sub>H<sub>36</sub>N<sub>2</sub>O<sub>3</sub>SNa requires 383.2339) 383.2351; anal (C<sub>18</sub>H<sub>36</sub>N<sub>2</sub>O<sub>3</sub>S requires C, 60.0, H, 10.1, N, 7.8) C, 59.9, H, 10.2, N, 7.7.

25   **Example 30: (S)-3-(Tetradecanesulfonyl)amino-caprolactam:**

(S)-3-amino-caprolactam hydrochloride **1** (2 mmol) and Na<sub>2</sub>CO<sub>3</sub> (6 mmol) in water (20 ml) were added to a solution of tetradecanesulfonylchloride (2 mmol) in dichloromethane (20 ml) at ambient temperature and the reaction was stirred for 10 hours. The organic layer was then separated and the aqueous phase was extracted

30   with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na<sub>2</sub>CO<sub>3</sub> and reduced *in vacuo*. The residue was purified by silica column chromatography (hexanes:EtOAc 3:1 to 100% EtOAc) and then by recrystallisation from heptane to give (S)-3-(tetradecanesulfonyl)amino-caprolactam (373 mg, 48%); m.p. 100-101 °C; [α]<sub>D</sub><sup>25</sup> (c = 1, CHCl<sub>3</sub>) +14.4; ν<sub>max</sub>/cm<sup>-1</sup> 3361, 3250 (NH),

1658 (CO), 1324, 1140 (SO<sub>2</sub>N); δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 6.64 (1H, t, J 6, CH<sub>2</sub>NH),  
 5.74 (1H, d, J 6, CHNH), 4.11 (1H, ddd, J 11.5, 6, 2, CHNH), 3.30-3.17 (2H, m,  
 CH<sub>2</sub>NH), 2.97-2.92 (2H, m, CH<sub>2</sub>SO<sub>2</sub>), 2.12-2.05 (1H, m, ring CH), 2.05-1.96 (1H,  
 m, ring CH), 1.87-1.59 (5H, m, CH<sub>2</sub>CH<sub>2</sub>SO<sub>2</sub> + 3 ring CH), 1.42-1.32 (3H, m, ring  
 5 CH + chain CH<sub>2</sub>), 1.32-1.18 (20H, m, chain CH<sub>2</sub>) and 0.86 (3H, m, CH<sub>3</sub>); δ<sub>C</sub> (125  
 MHz, CDCl<sub>3</sub>) 174.9 (CO) 55.5 (NHCHCO), 53.4 (CH<sub>2</sub>SO<sub>2</sub>), 42.2 (NCH<sub>2</sub>), 33.8,  
 31.9, 29.6 (×4), 29.5, 29.3 (×2), 29.1, 28.6, 28.3, 27.9, 23.5, 22.7 (CH<sub>2</sub>), and 14.1  
 (CH<sub>3</sub>); m/z (MNa<sup>+</sup> C<sub>20</sub>H<sub>40</sub>N<sub>2</sub>O<sub>3</sub>SNa requires 411.2652) 411.2655; anal (C<sub>20</sub>H<sub>40</sub>N<sub>2</sub>O<sub>3</sub>S  
 requires C, 61.8, H, 10.4, N, 7.2) C, 61.9, H, 10.5, N, 7.2.

10

**Example 31: (S)-3-(Hexadecanesulfonyl)amino-caprolactam:**

(S)-3-amino-caprolactam hydrochloride 1 (2 mmol) and Na<sub>2</sub>CO<sub>3</sub> (6 mmol) in water  
 (20 ml) were added to a solution of hexadecanesulfonylchloride (2 mmol) in  
 dichloromethane (20 ml) at ambient temperature and the reaction was stirred for 10  
 15 hours. The organic layer was then separated and the aqueous phase was extracted  
 with additional dichloromethane (2 × 25 ml). The combined organic layers were  
 dried over Na<sub>2</sub>CO<sub>3</sub> and reduced *in vacuo*. The residue was purified by silica column  
 chromatography (hexanes:EtOAc 3:1 to 100% EtOAc) and then by recrystallisation  
 from heptane to give (S)-3-(hexadecanesulfonyl)amino-caprolactam (553 mg,  
 20 66%); m.p. 100-101 °C; [α]<sub>D</sub><sup>25</sup> (c = 1, CHCl<sub>3</sub>) +14.1; ν<sub>max</sub>/cm<sup>-1</sup> 3356, 3249 (NH),  
 1659 (CO), 1323, 1140 (SO<sub>2</sub>N); δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 6.55 (1H, t, J 6, CH<sub>2</sub>NH),  
 5.76 (1H, d, J 6, CHNH), 4.11 (1H, ddd, J 11.5, 6, 2, CHNH), 3.30-3.17 (2H, m,  
 CH<sub>2</sub>NH), 2.94 (2H, t, J 8, CH<sub>2</sub>SO<sub>2</sub>), 2.12-2.04 (1H, m, ring CH), 2.04-1.97 (1H, m,  
 ring CH), 1.87-1.58 (5H, m, CH<sub>2</sub>CH<sub>2</sub>SO<sub>2</sub> + 3 ring CH), 1.42-1.32 (3H, m, ring CH  
 + chain CH<sub>2</sub>), 1.32-1.18 (24H, m, chain CH<sub>2</sub>) and 0.86 (3H, m, CH<sub>3</sub>); δ<sub>C</sub> (125 MHz,  
 25 CDCl<sub>3</sub>) 174.9 (CO) 55.5 (NHCHCO), 53.5 (CH<sub>2</sub>SO<sub>2</sub>), 42.1 (NCH<sub>2</sub>), 33.8, 31.9, 29.7  
 (×2), 29.6 (×4), 29.5, 29.3 (×2), 29.1, 28.6, 28.3, 27.9, 23.5, 22.7 (CH<sub>2</sub>), and 14.1  
 (CH<sub>3</sub>); m/z (MNa<sup>+</sup> C<sub>20</sub>H<sub>40</sub>N<sub>2</sub>O<sub>3</sub>SNa requires 439.2965) 439.2980; anal (C<sub>22</sub>H<sub>44</sub>N<sub>2</sub>O<sub>3</sub>S  
 requires C, 63.4, H, 10.6, N, 6.7) C, 63.1, H, 10.6, N, 6.6.

30

**Example 32: (S)-3-(Octadecanesulfonyl)amino-caprolactam:**

(S)-3-amino-caprolactam hydrochloride 1 (2 mmol) and Na<sub>2</sub>CO<sub>3</sub> (6 mmol) in water  
 (20 ml) were added to a solution of octadecanesulfonylchloride (2 mmol) in  
 dichloromethane (20 ml) at ambient temperature and the reaction was stirred for 10

hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane ( $2 \times 25$  ml). The combined organic layers were dried over  $\text{Na}_2\text{CO}_3$  and reduced *in vacuo*. The residue was purified by silica column chromatography (hexanes:EtOAc 3:1 to 100% EtOAc) and then by recrystallisation.

- 5 from heptane to give (*S*)-3-(octadecanesulfonyl)amino-caprolactam (545 mg, 61%); m.p. 99-100 °C;  $\nu_{\text{max}}/\text{cm}^{-1}$  3356, 3249 (NH), 1659 (CO), 1323, 1140 (SO<sub>2</sub>N);  
 $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 6.15 (1H, t, *J* 6, CH<sub>2</sub>NH), 5.69 (1H, d, *J* 6, CHNH), 4.12 (1H, ddd, *J* 11.5, 6, 2, CHNH), 3.30-3.18 (2H, m, CH<sub>2</sub>NH), 2.97-2.92 (2H, m, CH<sub>2</sub>SO<sub>2</sub>),  
2.12-2.07 (1H, m, ring CH), 2.06-1.97 (1H, m, ring CH), 1.87-1.56 (5H, m,  
10 CH<sub>2</sub>CH<sub>2</sub>SO<sub>2</sub> + 3 ring CH), 1.42-1.32 (3H, m, ring CH + chain CH<sub>2</sub>), 1.32-1.18 (28H, m, chain CH<sub>2</sub>) and 0.86 (3H, m, CH<sub>3</sub>):

**Example 33:** (S)-aminocaprolactam-Glycine-(L)-N(Boc)-Tryptophan:

This tripeptide was made on a solid-phase automated peptide synthesiser using (S)-aminocaprolactam for the final peptide coupling step.  $\text{Mr}(\text{Calc}) = 471.5110$

Observed Mr by mass spectrometry 471.6. Purity (%TIC in molecular ion peak) = 90%

**Example 34:** (S)-aminocaprolactam-(L)-valine-(L)-Desaminotryptophan

This tripeptide was made on a solid-phase automated peptide synthesiser using (S)-aminocaprolactam for the final peptide coupling step.  $\text{Mr}(\text{Calc}) = 398.4600$

Observed Mr by mass spectrometry 398.3. Purity (%TIC in molecular ion peak) = 96%

**Examples 35-38 of Intermediate Compounds useful in the synthesis of compounds of the invention:**

**Example 35:**

## Intermediate

- 15 (E)-Methyl 2,2-dimethyl-dodec-4-enoate:**

butyllithium (3.8 M, 10 mmol) was added to a solution of diisopropylamine (1.42 ml, 10 mmol) in dry THF at -78 °C under N<sub>2</sub>. The reaction was stirred at -78 °C for 20 minutes and then methyl isobutyrate (1.15 ml, 10 mmol) was added. The reaction was stirred at -78 °C for 1 hour, and then (*E*)-dec-2-enyl bromide (2.19 g,

10 mmol) was added and the reaction was allowed to warm to ambient temperature over 14 hours. The reaction solvent was then removed *in vacuo*, and the residue was partitioned between pH 2 aqueous buffer (0.5 M NaHSO<sub>4</sub> / 0.5 M Na<sub>2</sub>SO<sub>4</sub>) (100 ml) and hexane (3 × 100 ml). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and the hexane solvent removed *in vacuo* to give crude (*E*)-methyl 2,2-dimethyl-dodec-4-enoate (>90% pure) (2.27 g) as a colourless oil;  $\nu_{\text{max}}/\text{cm}^{-1}$  1734 (CO);  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 5.42 (1H, br dt, *J* 15, 6.5, CH=CH), 5.30 (1H, dtt, *J* 15, 7, 1, CH=CH), 3.64 (3H, s, OCH<sub>3</sub>), 2.18 (2H, dd, *J* 7, 1, CH<sub>2</sub>CMe<sub>2</sub>), 1.96 (2H, br q, *J* 6.5, CH<sub>2</sub>CH<sub>2</sub>CH=CH), 1.35-1.20 (10H, m, (CH<sub>2</sub>)<sub>5</sub>CH<sub>3</sub>), 1.14 (6H, s, C(CH<sub>3</sub>)<sub>2</sub>), 0.87 (3H, t, *J* 6.5, CH<sub>2</sub>CH<sub>3</sub>);  $\delta_{\text{C}}$  (125 MHz, CDCl<sub>3</sub>) 178.2 (CO), 134.1, 125.2 (HC=CH), 51.5 (OCH<sub>3</sub>), 43.6 (CH<sub>2</sub>), 42.6 (Me<sub>2</sub>CCO), 32.6, 31.8, 29.5, 29.1, 29.0 (CH<sub>2</sub>), 24.7 (C(CH<sub>3</sub>)<sub>2</sub>), 22.6 (CH<sub>2</sub>), 14.1 (CH<sub>2</sub>CH<sub>3</sub>); m/z (MH<sup>+</sup> C<sub>15</sub>H<sub>29</sub>N<sub>2</sub>O<sub>2</sub> requires 241.2168) 241.2169.

15     **Example 36:**

**Intermediate**

**(*E*)-2,2-Dimethyl-dodec-4-enoyl chloride:**

the entire product from the above reaction was then dissolved in ethanol (50 ml) and added to a solution of NaOH (2.0 g, 50 mmol) in water (25 ml). The mixture 20 was heated at reflux for 6 hours, allowed to cool and the solvents were then removed *in vacuo*. The residue was partitioned between pH 2 aqueous buffer (0.5 M NaHSO<sub>4</sub> / 0.5 M Na<sub>2</sub>SO<sub>4</sub>) (100 ml) and diethyl ether (3 × 100 ml). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and the ether solvent removed *in vacuo* to give crude (*E*)-2,2-dimethyl-dodec-4-enoyl acid (>90% pure) as a colourless oil;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 5.46 (1H, br dt, *J* 15, 6.5, CH=CH), 5.35 (1H, dtt, *J* 15, 7, 1, CH=CH), 2.22 (2H, dd, *J* 7, 1, CH<sub>2</sub>CMe<sub>2</sub>), 1.98 (2H, br q, *J* 6.5, CH<sub>2</sub>CH<sub>2</sub>CH=CH), 1.37-1.21 (10H, m, (CH<sub>2</sub>)<sub>5</sub>CH<sub>3</sub>), 1.17 (6H, s, C(CH<sub>3</sub>)<sub>2</sub>), 0.87 (3H, t, *J* 6.5, CH<sub>2</sub>CH<sub>3</sub>). The crude acid was dissolved in dichloromethane (50 ml) and oxalyl chloride (3 ml) 25 was added along with a drop of DMF. The reaction was stirred for 1 hour and the solvent was removed *in vacuo* to give crude (*E*)-2,2-dimethyl-dodec-4-enoyl chloride which was all used without purification in the next step.

**Example 37:****Intermediate****Methyl 2,2,5-trimethyl-hex-4-enoate:**

butyllithium (2.9 M, 50 mmol) was added to a solution of diisopropylamine (7.2

- 5 ml, 50 mmol) in dry THF (200 ml) at -78 °C under N<sub>2</sub>. The reaction was stirred at -78 °C for 20 minutes and then methyl isobutyrate (5.7 ml, 50 mmol) was added. The reaction was stirred at -78 °C for 1 hour, and then 3-methyl-but-2-enyl bromide (5.8 ml, 50 mmol) was added and the reaction was allowed to warm to ambient temperature over 14 hours. The reaction solvent was then removed *in vacuo*, and  
 10 the residue was partitioned between pH 2 aqueous buffer (0.5 M NaHSO<sub>4</sub> / 0.5 M Na<sub>2</sub>SO<sub>4</sub>) and hexane (3 × 250 ml). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and the hexane solvent removed *in vacuo* to give methyl 2,2,5-trimethyl-hex-4-enoate as a colourless oil (6.93 g 81%);  $\nu_{\text{max}}$ /cm<sup>-1</sup> 1732 (CO);  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 5.04 (1H, tsept, *J* 7.5, 1.5, CH=C), 3.63 (3H, s, OCH<sub>3</sub>), 2.20 (2H, d, *J* 7.5,  
 15 CHCH<sub>2</sub>), 1.68 (3H, br s, CH=CMeMe), 1.58 (3H, br s, CH=CMeMe), 1.14 (6H, s, (CH<sub>3</sub>)<sub>2</sub>CO);  $\delta_{\text{C}}$  (125 MHz, CDCl<sub>3</sub>) 178.4 (CO), 134.1 (Me<sub>2</sub>C=CH), 119.8 (Me<sub>2</sub>C=CH), 51.6 (OCH<sub>3</sub>), 42.8 (Me<sub>2</sub>CCO), 38.7 (CH<sub>2</sub>), 25.9, 24.7 (× 2), 17.8 (CCH<sub>3</sub>); m/z (MH<sup>+</sup> C<sub>10</sub>H<sub>19</sub>O<sub>2</sub> requires 171.1385) 171.1388.

**Example 38:****Intermediate****2,2,5-Trimethyl-hex-4-enoyl chloride:**

methyl 2,2,5-trimethyl-hex-4-enoate (2.74 g, 16 mmol) was dissolved in ethanol

- (50 ml) and added to a solution of NaOH (3.0 g, 75 mmol) in water (35 ml). The mixture was heated at reflux for 6 hours, allowed to cool and the solvents were then  
 25 removed *in vacuo*. The residue was partitioned between pH 2 aqueous buffer (0.5 M NaHSO<sub>4</sub> / 0.5 M Na<sub>2</sub>SO<sub>4</sub>) and diethyl ether (3 × 150 ml). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and the ether solvent removed *in vacuo* to give crude 2,2,5-trimethyl-hex-4-enoyl chloride (>95% pure) as a colourless oil;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 5.12 (1H, tsept, *J* 7.5, 1.5, CH=C), 2.25 (2H, d, *J* 7.5, CHCH<sub>2</sub>), 1.71 (3H, br  
 30 s, CH=CMeMe), 1.60 (3H, br s, CH=CMeMe), 1.18 (6H, s, (CH<sub>3</sub>)<sub>2</sub>CO). The crude acid was dissolved in dichloromethane (50 ml) and oxalyl chloride (3 ml) was added along with a drop of DMF. The reaction was stirred for 1 hour and the

solvent was removed *in vacuo* to give crude 2,2,5-trimethyl-hex-4-enoyl chloride which was all used without purification in the next step.

**Example 39:**

This compound has two head groups on either side of a 2,2,6,6 tetramethyl heptanoic acid. It is in effect a dimer of the corresponding 2,2-dimethyl compound of the invention:

***(S,S) N,N'-bis-(2'-oxo-azepan-3'-yl) 2,2,6,6-tetramethylheptadiamide:***

- 5   (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate 2 (2 mmol) and Na<sub>2</sub>CO<sub>3</sub> (6 mmol) in water (25 ml) were added to a solution of 2,2,6,6-tetramethyl-heptandioyl dichloride (1 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na<sub>2</sub>CO<sub>3</sub> and reduced *in vacuo*. The residue was purified by recrystallisation from EtOAc to give (S,S)-dimer (199 mg, 46%); m.p. 234-236 °C; [α]<sub>D</sub><sup>25</sup> (c = 1, CHCl<sub>3</sub>) +29.4; ν<sub>max</sub>/cm<sup>-1</sup> 3379, 3255 (NH), 1683, 1637 (CO), 1507, 1497 (NH); δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 7.07 (2H, d, J 5.5, CHNH), 6.42 (2H, br s, CH<sub>2</sub>NH), 4.44 (2H, ddd, J 11, 5.5, 1.5, CHNH), 3.31-15 3.17 (4H, m, CH<sub>2</sub>NH), 2.04-1.94 (4H, m, ring CH), 1.86-1.73 (4H, m, ring CH), 1.51-1.31 (8H, br m, 2 × ring CH + CH<sub>2</sub>CMe<sub>2</sub>) and 1.12 (14H, m, chain CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub> + CMe<sub>2</sub>); δ<sub>C</sub> (125 MHz, CDCl<sub>3</sub>) 176.9, 175.9 (CO), 52.1 (NHCH), 42.0 (CMe<sub>2</sub>), 42.1, 41.5, 31.5, 28.9, 28.0 (CH<sub>2</sub>), 25.3, 25.1 (CH<sub>3</sub>) and 20.0 (CH<sub>2</sub>); m/z (M<sup>+</sup> C<sub>23</sub>H<sub>40</sub>N<sub>4</sub>O<sub>4</sub> requires 436.30496) 436.30437.

**Example 40: (S)-3-(1',1'-dimethylundecanoyl)amino-caprolactam**

This compound is the sulfonamide analogue of Example 12.

20   **Pharmacological study of the products of the invention**

**Inhibition of MCP-1 induced leukocyte migration**

***Assay principle***

The biological activity of the compounds of the current invention may be demonstrated using any of a broad range of functional assays of leukocyte

25   migration *in vitro*, including but not limited to Boyden chamber and related

transwell migration assays, under-agarose migration assays and direct visualisation chambers such as the Dunn Chamber.

- For example, to demonstrate the inhibition of leukocyte migration in response to
- 5 chemokines (but not other chemoattractants) the 96-well format micro transwell assay system from Neuroprobe (Gaithersburg, MD, USA) has been used. In principle, this assay consists of two chambers separated by a porous membrane.
- 10 The chemoattractant is placed in the lower compartment and the cells are placed in the upper compartment. After incubation for a period at 37°C the cells move towards the chemoattractant, and the number of cells in the lower compartment is proportional to the chemoattractant activity (relative to a series of controls).

This assay can be used with a range of different leukocyte populations. For example, freshly prepared human peripheral blood leukocytes may be used.

- 15 Alternatively, leukocyte subsets may be prepared, including polymorphonuclear cells or lymphocytes or monocytes using methods well known to those skilled in the art such as density gradient centrifugation or magnetic bead separations.
- Alternatively, immortal cell lines which have been extensively validated as models of human peripheral blood leukocytes may be used, including, but not limited to
- 20 THP-1 cells as a model of monocytes or Jurkat cells as model of naïve T cells.

Although a range of conditions for the assay are acceptable to demonstrate the inhibition of chemokine-induced leukocyte migration, a specific example is hereby provided.

25

#### *Materials*

The transwell migration systems are manufactured by Neuroprobe, Gaithersburg, MD, USA.

- 30 The plates used are ChemoTx plates (Neuroprobe 101-8) and 30 µl clear plates (Neuroprobe MP30).

Geys' Balanced Salt Solution is purchased from Sigma (Sigma G-9779).

Fatty acid-free BSA is purchased from Sigma (Sigma A-8806).

MTT, i.e. 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, is purchased from Sigma (Sigma M-5655).

RPMI-1640 without phenol red is purchased from Sigma (Sigma R-8755). The THP-1 cell line (European Cell culture Collection) were used as the leukocyte cell population.

5    *Test protocol*

The following procedure is used for testing the invention compounds for MCP-1 induced leukocyte migration:

First, the cell suspension to be placed in the upper compartment is prepared. The  
10    THP-1 cells are pelleted by centrifugation (770 x g; 4 mins) and washed with Geys  
Balanced Salt Solution with 1mg/ml BSA (GBSS + BSA). This wash is then  
repeated, and the cells repelleted before being resuspended in a small volume of  
GBSS + BSA for counting, for example using a standard haemocytometer.

15    The volume of GBSS + BSA is then adjusted depending on the number of cells  
present so that the cells are at final density of  $4.45 \times 10^6$  cells per ml of GBSS +  
BSA. This ensures that there are 100,000 THP-1 cells in each 25 $\mu$ l of the solution  
that will be placed in the upper chamber of the plate.

20    To test a single compound for its ability to inhibit MCP-1 induced migration, it is  
necessary to prepare two lots of cells. The suspension of THP-1 cells at  $4.45 \times 10^6$   
cells/ml is divided into two pots. To one pot the inhibitor under test is added at an  
appropriate final concentration, in an appropriate vehicle (for example at 1 $\mu$ M in  
not more than 1% DMSO). To the second pot an equal volume of GBSS + BSA  
25    plus vehicle as appropriate (e.g. not more than 1% DMSO) is added to act as a  
control.

Next, the chemoattractant solution to be placed in the lower compartment is  
prepared. MCP-1 is diluted in GBSS + BSA to give a final concentration of  
30    25 ng/ml. This is divided into two pots, as for the cell suspension. To one pot, the  
test compound is added to the same final concentration as was added to the cell  
suspension, while to the other pot an equal volume of GBSS + BSA plus vehicle as  
appropriate (e.g. not more than 1% DMSO) is added.

Note that the volume of liquid that needs to be added to make the addition of the test compound needs to be taken into account, when establishing the final concentration of MCP-1 in the solution for the lower compartment and the final concentration of cells in the upper compartment.

5

Once the chemoattractant solutions for the lower wells and cell solutions for the upper chambers have been prepared, the migration chamber should be assembled.

Place 29 µl of the appropriate chemoattractant solution into the lower well of the chamber. Assays should be performed with at least triplicate determinations of

10 each condition. Once all the lower chambers have been filled, apply the porous membrane to the chamber in accordance with the manufacturer's instructions.

Finally, apply 25 µl of the appropriate cell solution to each upper chamber. A plastic lid is placed over the entire apparatus to prevent evaporation.

15 The assembled chamber is incubated at 37 °C, 5% CO<sub>2</sub>, for 2 hours. A suspension of cells in GBSS + BSA is also incubated under identical conditions in a tube: these cells will be used to construct a standard curve for determining the number of cells that have migrated to the lower chamber under each condition.

20 At the end of the incubation, the liquid cell suspension is gently removed from the upper chamber, and 20µl of ice-cold 20mM EDTA in PBS is added to the upper chamber, and the apparatus is incubated at 4°C for 15 mins. This procedure causes any cells adhering to the underside of the membrane to fall into the lower chamber.

25 After this incubation the filter is carefully flushed with GBSS + BSA to wash off the EDTA, and then the filter is removed.

The number of cells migrated into the lower chamber under each condition can then be determined by a number of methods, including direct counting, labelling with

30 fluorescent or radioactive markers or through the use of a vital dye. Typically, we utilise the vital dye MTT. 3 µl of stock MTT solution are added to each well, and then the plate is incubated at 37 °C for 1-2 hours during which time dehydrogenase enzymes within the cells convert the soluble MTT to an insoluble blue formazan product that can be quantified spectrophotometrically.

In parallel, an 8-point standard curve is set up. Starting with the number of cells added to each upper chamber (100,000) and going down in 2-fold serial dilutions in GBSS + BSA, the cells are added to a plate in 25 µl, with 3 µl of MTT stock solution added.

The standard curve plate is incubated along side the migration plate.

At the end of this incubation, the liquid is carefully removed from the lower chambers, taking care not to disturb the precipitated formazan product. After allowing to air dry briefly, 20µl of DMSO is added to each lower chamber to solubilise the blue dye, and absorbance at 595nm is determined using a 96-well plate reader. The absorbance of each well is then interpolated to the standard curve to estimate the number of cells in each lower chamber.

The MCP-1 stimulated migration is determined by subtracting the average number of cells that reached the lower compartment in wells where no MCP-1 was added from the average number of cells that reached the lower compartment where MCP-1 was present at 25ng/ml.

The impact of the test substance is calculated by comparing the MCP-1-induced migration which occurred in the presence or absence of various concentrations of the test substance. Typically, the inhibition of migration is expressed as a percentage of the total MCP-1 induced migration which was blocked by the presence of the compound. For most compounds, a dose-response graph is constructed by determining the inhibition of MCP-1 induced migration which occurs at a range of different compound concentrations (typically ranging from 1nM to 1µM or higher in the case of poorly active compounds). The inhibitory activity of each compound is then expressed as the concentration of compound required to reduce the MCP-1-induced migration by 50% (the ED<sub>50</sub> concentration).

*Results*

The compounds of examples 1 to 7 and 9 to 34 and 39 were tested and were shown to have an ED<sub>50</sub> of 100 nM or less in this test.

5   *Enantioselectivity*

The (S)- and (R)- enantiomers of three different members of the aminocaprolactam series were synthesised to determine whether the biological activity showed enantioselectivity.

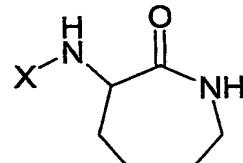
- 10   The comparison was made between the compounds of examples 1 and 7, between the compounds of examples 10 and 11, and between the compounds of examples 12 and 17.

- 15   The dose-response curves for each of the four compounds of examples 1, 7, 10 and 11 as inhibitors of MCP-1 induced THP-1 cell migration were determined using the transwell migration assay and are shown in Figure 1. In both cases, the (S)-enantiomer was significantly (10-50 fold) more active than the (R)-enantiomer. Very similar data was obtained using the compounds of examples 12 and 17, such that the (S)-enantiomer was significantly (10-50 fold) more active than the (R)-enantiomer.
- 20

- These data, for three example members of the aminocaprolactam series, demonstrate that for the application of the compounds of the present invention as anti-inflammatory agents in vivo it is preferable to use the pure (S)-enantiomer of the compound, rather than the racemic mixture of the two enantiomers or the pure (R)-enantiomer.
- 25

Claims

1. Use of a compound of general formula (I) or a pharmaceutically acceptable salt thereof, for the preparation of a medicament intended to treat an inflammatory disorder:



(I)

wherein

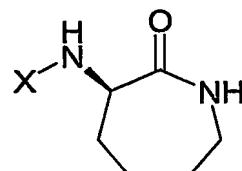
X is -CO-R<sup>1</sup> or -SO<sub>2</sub>-R<sup>2</sup>,

R<sup>1</sup> is an alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl or alkylamino radical of 4 to 20 carbon atoms (for example of 5 to 20 carbon atoms, of 8 to 20 carbon atoms, of 9 to 20 carbon atoms, of 10 to 18 carbon atoms, of 12 to 18 carbon atoms, of 13 to 18 carbon atoms, of 14 to 18 carbon atoms, of 13 to 17 carbon atoms.); and

R<sup>2</sup> is an alkyl radical of 4 to 20 carbon atoms (for example of 5 to 20 carbon atoms, of 8 to 20 carbon atoms, of 9 to 20 carbon atoms, of 10 to 18 carbon atoms, of 12 to 18 carbon atoms, of 13 to 18 carbon atoms, of 14 to 18 carbon atoms, and of 13 to 17 carbon atoms); or

alternatively R<sup>1</sup> and R<sup>2</sup> are selected independently from a peptido radical having from 1 to 4 peptidic moieties linked together by peptide bonds.

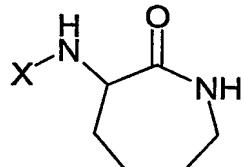
2. Use of a compound of formula (I') or a pharmaceutically acceptable salt thereof, for the preparation of a medicament intended to treat an inflammatory disorder:



(I')

wherein X has the same meaning as above.

3. A pharmaceutical composition comprising, as active ingredient, a compound of formula (I) or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient and/or carrier:
- 5

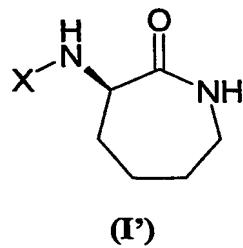


(I)

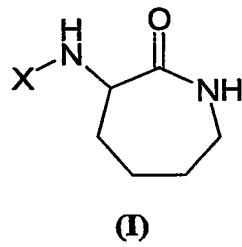
wherein

X is -CO-R<sup>1</sup> or -SO<sub>2</sub>-R<sup>2</sup>,

- 10 R<sup>1</sup> is an alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl or alkylamino radical of 4 to 20 carbon atoms (for example of 5 to 20 carbon atoms, of 8 to 20 carbon atoms, of 9 to 20 carbon atoms, of 10 to 18 carbon atoms, of 12 to 18 carbon atoms, of 13 to 18 carbon atoms, of 14 to 18 carbon atoms, of 13 to 17 carbon atoms.); and
- 15 R<sup>2</sup> is an alkyl radical of 4 to 20 carbon atoms (for example of 5 to 20 carbon atoms, of 8 to 20 carbon atoms, of 9 to 20 carbon atoms, of 10 to 18 carbon atoms, of 12 to 18 carbon atoms, of 13 to 18 carbon atoms, of 14 to 18 carbon atoms, and of 13 to 17 carbon atoms); or
- 20 alternatively R<sup>1</sup> and R<sup>2</sup> may be selected independently from a peptido radical having from 1 to 4 peptidic moieties linked together by peptide bonds (for example a peptido radical of 1 to 4 amino acid residues).
4. A pharmaceutically acceptable composition comprising active ingredient, a
- 25 compound of formula (I') or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient and/or carrier:



5. A compound of general formula (I):



wherein

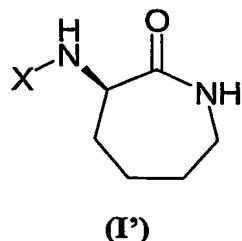
- 5    X is -CO-R<sup>1</sup> or -SO<sub>2</sub>-R<sup>2</sup>,

R<sup>1</sup> is an alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl or alkylamino radical of 4 to 20 carbon atoms (for example of 5 to 20 carbon atoms, of 8 to 20 carbon atoms, of 9 to 20 carbon atoms, of 10 to 18 carbon atoms, of 12 to 18 carbon atoms, of 13 to 18 carbon atoms, of 14 to 18 carbon atoms, of 13 to 17 carbon atoms.); and

R<sup>2</sup> is an alkyl radical of 4 to 20 carbon atoms (for example of 5 to 20 carbon atoms, of 8 to 20 carbon atoms, of 9 to 20 carbon atoms, of 10 to 18 carbon atoms, of 12 to 18 carbon atoms, of 13 to 18 carbon atoms, of 14 to 18 carbon atoms, and of 13 to 17 carbon atoms); or

alternatively R<sup>1</sup> and R<sup>2</sup> are selected independently from a peptido radical having from 1 to 4 peptidic moieties linked together by peptide bonds.

6. A compound of general formula (I'):



wherein X has the same meaning as above.

7. Compounds, compositions and uses of the compounds of general formula (I) or

5       or (I'), or their pharmaceutically acceptable salts, according to any preceding claim, wherein the alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl or alkylamino part of the R<sup>1</sup> radical is either linear or is branched but contains a linear chain of at least 8 or at least 10 carbon atoms.

10      8. Compounds, compositions and uses according to claim 7 wherein the R<sup>1</sup> radical has an alpha-carbon (2-position in X) which is di-substituted with the same or different groups selected from: alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl and alkylamino radicals.

15      9. Compounds, compositions and uses according to claim 8 wherein the alpha-carbon is chiral.

10. Compounds, compositions and uses according to claim 9 wherein the alpha-carbon has sp<sup>3</sup> hybridised bonds.

20

11. Compounds, compositions and uses according to claim 9 wherein the alpha-carbon has essentially tetrahedral bond angles.

12. A use according to claim 1 or a pharmaceutical composition according to claim  
25 3, or a compound according to claim 5, wherein the compound is selected from the group consisting of:

- (S)-3-hexadecanoylamino-caprolactam;
- (S)-3-undecanoylamino-caprolactam;
- (S)-3-(undec-10-enoyl)amino-caprolactam;

- (S)-3-(undec-10-ynoyl)amino-caprolactam;
  - (S)-3-dodecanoylamino-caprolactam;
  - (S)-3-tetradecanoylamino-caprolactam;
  - (R)-3-hexadecanoylamino-caprolactam;
  - 5 - (S)-3-octadecanoylamino-caprolactam;
  - (S)-(Z)-3-(hexadec-9-enoyl)amino-caprolactam;
  - (S)-(Z)-3-(octadec-9-enoyl)amino-caprolactam;
  - (R)-(Z)-3-(octadec-9-enoyl)amino-caprolactam;
  - (S)-3-(2',2'-dimethyl-dodecanoyl)amino-caprolactam;
  - 10 - (S)-3-(decyloxycarbonyl)amino-caprolactam;
  - (S)-(E)-3-(dodec-2-enoyl)amino-caprolactam;
  - (S)-3-(dec-9-enylaminocarbonyl)amino-caprolactam;
  - (S)-3-(decylaminocarbonyl)amino-caprolactam;
- and pharmaceutically acceptable salts thereof.

15

13. A use according to claim 1, or a pharmaceutical composition according to claim 3, or a compound according to claim 5 wherein the compound is selected from the group consisting of: (S)-3-hexadecanoylamino-caprolactam, (S)-3-(2',2'-dimethyl-dodecanoyl)amino-caprolactam and pharmaceutically acceptable salts thereof.

20

14. A use according to claim 1, or a pharmaceutical composition according to claim 3, or a compound according to claim 5, wherein the compound is selected from the group consisting of:

- 25 - (R)-3-(2',2'-Dimethyl-dodecanoyl)amino-caprolactam;
- (S)-3-(2',2'-Dimethyl-pentanoyl)amino-caprolactam;
- (S)-3-(2',2'-Dimethyl-pent-4-enoyl)amino-caprolactam;
- (S)-3-(2',2'-Dimethyl-propionyl)amino-caprolactam;
- (S)-3-(2',2'-Dimethyl-butyryl)amino-caprolactam;
- 30 - (S,E)-3-(2',2'-Dimethyl-dodec-4'-enoyl)amino-caprolactam;
- (S)-3-(2',2',5'-Trimethyl-hex-4'-enoyl)amino-caprolactam;
- (S)-3-(2',2',5'-Trimethyl-hexanoyl)amino-caprolactam;
- (S)-3-(11'-bromo-undecanoyl)amino-caprolactam;
- (S)-3-(11'-azido-undecanoyl)amino-caprolactam;

- (S) Sodium 3-(undecanoyl)amino-caprolactam 11'-sulfonate tetrahydrate;
  - (S)-3-(Decanesulfonyl)amino-caprolactam;
  - (S)-3-(Dodecanesulfonyl)amino-caprolactam;
  - (S)-3-(Tetradecanesulfonyl)amino-caprolactam;
  - 5 - (S)-3-(Hexadecanesulfonyl)amino-caprolactam;
  - (S)-3-(Octadecanesulfonyl)amino-caprolactam;  
and pharmaceutically acceptable salts thereof.
15. Use of a compound of formula (I) or (I') according to one of claims 1, 2, 12, 13  
10 and 14 wherein the inflammatory disorder is selected from the group consisting of autoimmune diseases, vascular disorders, viral infection or replication, asthma, osteoporosis (low bone mineral density), tumor growth, rheumatoid arthritis, organ transplant rejection and/or delayed graft or organ function, a disorder characterised by an elevated TNF- $\alpha$  level, psoriasis, skin wounds, disorders caused by  
15 intracellular parasites, allergies, Alzheimer's disease, antigen induced recall response, immune response suppression, multiple sclerosis, ALS, fibrosis, and formation of adhesions.
16. A method of treatment, amelioration or prophylaxis of the symptoms of an  
20 inflammatory disease (including an adverse inflammatory reaction to any agent) by the administration to a patient of an anti-inflammatory amount of a compound, composition or medicament as claimed in any of claims 1 to 14.
17. Compounds, compositions, and uses of the compounds of general formula (I)  
25 or (I'), or their pharmaceutically acceptable salts, or a method of treatment according to any preceding claim wherein the substituent R<sup>1</sup> is not a straight chain alkyl group.
18. Compounds, compositions, and uses of the compounds of general formula (I)  
30 or (I'), or their pharmaceutically acceptable salts, or a method of treatment according to any preceding claim wherein the substituent R<sup>1</sup> is a branched chain alkyl group.

19. Compounds, compositions, and uses of the compounds of general formula (I) or (I'), or their pharmaceutically acceptable salts, or a method of treatment according to any preceding claim wherein the substituent R<sup>1</sup> is not an alkyl group.
- 5    20. A pharmaceutical composition for treatment of an inflammatory disorder comprising, as active ingredient, (*S,S*) *N,N*-bis-(2'-oxo-azepan-3'-yl) 2,2,6,6-tetramethylheptadiamide or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient and/or carrier.
- 10    21. A synthetic intermediate, useful in the synthesis of compounds of general formula (I) or (I'), selected from the group consisting of:  
- (*E*)-Methyl 2,2-dimethyl-dodec-4-enoate;  
- (*E*)-2,2-Dimethyl-dodec-4-enoyl chloride;  
- Methyl 2,2,5-trimethyl-hex-4-enoate;  
15    - 2,2,5-Trimethyl-hex-4-enoyl chloride;  
and pharmaceutically acceptable salts thereof.
22. A use according to claim 1, or a pharmaceutical composition according to claim 3, or a compound according to claim 5, wherein the compound is  
20    (*S*)-3-(1',1'-dimethylundecanoyl)amino-caprolactam or a pharmaceutically acceptable salt thereof.

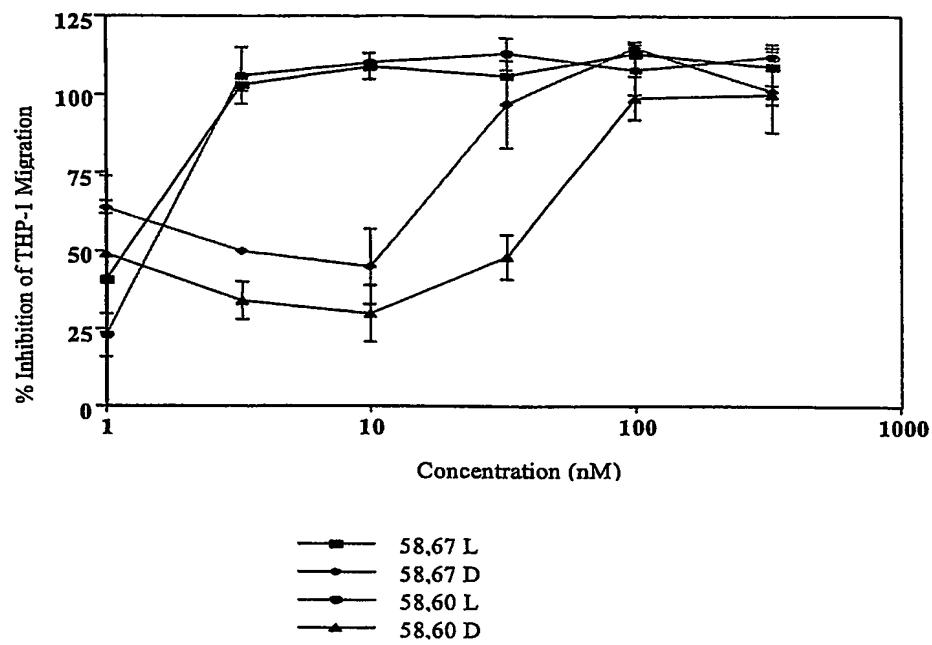


FIGURE 1

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